EXHIBIT 11

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION THIS DOCUMENT RELATES TO ALL CASES	Civil Action No. 3:16-md-2738-FLW-LHG MDL No. 2328

RULE 26 REPORT OF MICHAEL M. CROWLEY, PhD REGARDING THE FRAGRANCE CHEMICAL CONSTITUENTS IN JOHNSON & JOHNSON TALCUM POWDER PRODUCTS

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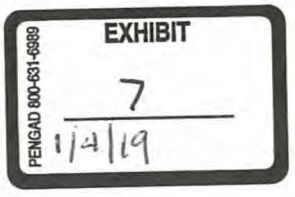
November 12, 2018



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Abbreviation	Definition or Explanation
Allergen	An allergen is a type of antigen that produces an abnormally vigorous immune response in which the immune system fights off a perceived threat that would otherwise be harmless to the body.
ACS	American Chemical Society
The Cosmetic Ingredient Review (CIR)	The Cosmetic Ingredient Review (CIR) reviews and assesses the safety of ingredients used in cosmetics in and publishes the results in the peer-reviewed scientific literature. The Cosmetic Ingredient Review was established in 1976 by the industry trade association (then the Cosmetic, Toiletry, and Fragrance Association, now the Personal Care Products Council (PCPC)..
CAS Number	CAS stands for "Chemical Abstracts Service," a division of the American Chemical Society that provides comprehensive electronic chemical information services. CAS assigns unique CAS Registry Numbers to chemical substances. The CAS Registry Number itself has no chemical significance.
CFR	Code of Federal Regulations. The Code of Federal Regulations is the codification of the general and permanent rules and regulations published in the Federal Register by the executive departments and agencies of the federal government of the United States.
CPSA	Consumer Product Safety Act, codified at 15 U.S.C. Section 2051–2084
FDA	The United States Food and Drug Administration
FEMA	The Flavor and Extract Manufacturers Association of the United States. FEMA is a trade association that has established expert panels that evaluate and make conclusions on the GRAS status of flavoring substances.
FEMA GRAS Program	In 1959, The Flavor and Extract Manufacturers Association of the United States (FEMA) took its initial actions to establish a program to assess the safety and "GRAS" (generally recognized as safe) status of flavor ingredients as described in the 1958 Food Additives Amendments to the Federal Food, Drug, and Cosmetic Act, the Federal law governing the regulation of flavors and other food ingredients. Since then, the FEMA GRAS program has become the longest-running and most widely recognized industry GRAS assessment program.
FFDCA	Federal Food, Drug, and Cosmetic Act, codified at 21 U.S.C. Section 321–397
FHSA	Federal Hazardous Substances Act, codified as amended at 15 U.S.C. Section 1261–1273
GRAS	Generally Recognized As Safe

Abbreviation	Definition or Explanation
	Generally recognized as safe is an American Food and Drug Administration (FDA) designation that a chemical or substance added to food is considered safe by experts, and so is exempted from the usual Federal Food, Drug, and Cosmetic Act (FFDCA) food additive tolerance requirements. The concept of food additives being "generally recognized as safe" was first described in the Food Additives Amendment of 1958, and all additives introduced after this time had to be evaluated by new standards. In the United States, the GRAS concept is one way in which the regulatory authority to use a food ingredient (other than color additives) can be determined with the other key path being through an application to the Food and Drug Administration for food additive status. GRAS status may be achieved either through the FDA's voluntary GRAS notification program (FDA, 1997) or through a properly conducted GRAS determination made by a private party. The statutory definition of GRAS has four key criteria, all of which must be met for a food ingredient to be considered generally recognized as safe and exempt from the requirements for food additive approval: • There must be general recognition of safety by qualified experts. • The experts must be qualified by training and experience to evaluate the substance's safety. • The experts must base their determination of safety on scientific procedures or on common use in food prior to 1958. • The determination of general recognition of safety must take into account the conditions of intended use for the substance, in other words its function in the food, e.g. flavoring.
GHS hazard statements	Hazard statements from the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).
Hypersensitivity	A state of altered reactivity in which the body reacts with an exaggerated immune response to a foreign agent
IFRA	International Fragrance Association
Inactive Ingredient Database (IID)	The Inactive Ingredient Database provides information on inactive ingredients present in FDA-approved drug products. In general, inactive ingredients on this list have been subject to extensive toxicology studies for a given route of administration.
Irritant	Irritation, in biology and physiology, is a state of inflammation or painful reaction to allergy or cell-lining

Abbreviation	Definition or Explanation
	damage. A stimulus or agent which induces the state of irritation is an irritant.
JECFA	The Joint Expert Committee on Food Additives (JECFA) is an international expert scientific committee that is administered jointly by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO).
OSHA Hazard Communication Standard 29 CFR 1910.1200	Describes and classifies the hazards of all chemicals produced or imported. Contains information concerning the classified hazards transmitted to employers and employees. Intended to be consistent with the provisions of the United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Revision 3.
Photosensitivity	Photosensitivity is the amount to which an object reacts upon receiving photons, especially visible light. In medicine, the term is principally used for abnormal reactions of the skin, and two types are distinguished, photoallergy and phototoxicity.
Phototoxicity	Phototoxicity, also called photoirritation, is a chemically induced skin irritation, requiring light that does not involve the immune system.
PubChem	A database of chemical molecules and their activities against biological assays. The system is maintained by the National Center for Biotechnology Information, a component of the National Library of Medicine, which is part of the United States National Institutes of Health.
QRA	Quantitative Risk Assessment (QRA), an exposure based risk assessment system developed by IFRA to determine safe use levels of fragrances in consumer products.
REXPAN	RIFM Expert Panel. REXPAN examines the dermal effects, systemic toxicity and environmental consequences of the use of and exposure to fragrance materials
RIFM	Research Institute for Fragrance Materials, the science center of IFRA
RTECS	Registry of Toxic Effects of Chemical Substances. RTECS is a definitive toxicological database with supplemental information pertinent to both the chemical industry and the occupational safety and health community. This technical data is needed to assess workers' exposures to chemicals, particularly to lesser-known-and-used chemical substances. OSHA has designated RTECS as a primary source for toxicity data for Material Safety Data Sheets in its Hazard Communications Rule. In recent years RTECS has grown to include more than 160,000 chemicals. The toxicological data are organized into six fields: primary irritation, mutagenic effects, reproductive

Abbreviation	Definition or Explanation
	effects, tumorigenic effects, acute toxicity and multiple dose toxicity.
SCHER	Scientific Committee on Health and Environmental Risks is an independent scientific committee managed by the Directorate-General for Health and Consumer Protection of the European Commission, which provide scientific advice to the Commission on issues related to consumer products.
Sensitization	The preliminary exposure of a person to an allergen that leads to antibody production by the immune system and, on subsequent exposure, to an allergic or hypersensitivity reaction. Inducing an adaptive response in the immune system and or exposure to allergen that results in the development of hypersensitivity. In this sense, sensitization is the term more often in usage for induction of allergic responses.
ToxNet	TOXNET® (TOXicology Data NETwork) is a group of databases covering chemicals and drugs, diseases and the environment, environmental health, occupational safety and health, poisoning, risk assessment and regulations, and toxicology. It is managed by the Toxicology and Environmental Health Information Program (TEHIP) in the Division of Specialized Information Services (SIS) of the National Library of Medicine (NLM).
TSCA	Toxic Substances Control Act
UNII	UNII stands for "Unique Ingredient Identifier". The UNII is a part of the joint United States Pharmacopeia (USP)/FDA Substance Registration System (SRS), which has been designed to support health information technology initiatives by providing unique identifiers for substances in drugs, biologics, foods, and devices based on molecular structure and/or descriptive information. The SRS is used to generate permanent, unique, unambiguous identifiers for substances in regulated products

1 EXECUTIVE SUMMARY

This report addresses the fragrance components of Johnson and Johnson's talcum powder products and the question of whether these substances contribute to the development of ovarian cancer.

This report addresses these questions:

- Are the fragrance chemicals in compliance with governmental and industry standards?
- Can the fragrance chemicals in the talcum powder products contribute to the inflammatory properties, toxicity, and potential carcinogenicity of the products?

To answer these questions, I conducted an independent review of the regulatory standards, safety, toxicological, medical, pharmacological and other scientific literature concerning the fragrance chemicals present in Johnson's Baby Powder and Shower to Shower talcum products. Although I have experience in the vaginal administration of pharmaceutical products and its implications, I was asked, for the purposes of this report, to assume that talcum powder can migrate from the perineum to the upper genital tract. It is my understanding that other expert witnesses will address this topic.

Johnson's Baby Powder contains a mixture of 141 fragrance chemicals, some of which are extracts that are themselves a mixture of chemicals. Likewise, the Shower to Shower product contains a fragrance mixture comprising 53 fragrances, some of which are mixtures themselves. Of the 53 fragrance chemicals in Shower to Shower, 19 are present in Baby Powder (34 fragrance chemicals are unique to Shower to Shower). Thus, there are at least 175 fragrance chemicals between the two products.

The fragrance chemicals were examined for compliance to government and industry regulatory standards. Twenty-two (22) fragrance chemicals in the Johnson's Baby Powder (15.6% of those present) and twenty (20) fragrance chemicals in the Shower to Shower product (37.7%) were identified with a regulatory concern (Table 1).

There are chemicals in the fragrance mixture in the Johnson & Johnson talcum products that do not have an established government or industry standard, are not fragrances, or are not approved for use in a fragrance. For example, Myroxylon Pereirae (Balsam Peru) Oil, present in Baby Powder, is prohibited by the International Fragrance Association (IFRA) for use as a fragrance ingredient and on the EU Annex ii of chemicals prohibited from cosmetics in Europe. Para-cresol is not permitted in cosmetics according to the Cosmetic Ingredient Review Expert Panel.

In addition, Methyl Hydrogenated Rosinate is present in both the Baby Powder and Shower to Shower products. Methyl Hydrogenated Rosinate is not a fragrance, does not have an IFRA standard and is not listed by CIR.

Accordingly, in response to the first question, in my opinion the fragrance chemicals are not in compliance with governmental and industry standards.

The fragrance chemicals were reviewed for pharmacological activity, safety and toxicity concerns. Thirty-four chemicals were identified in Johnson's Baby Powder (24%) and twelve chemicals in the Shower to Shower product (20%) with safety and toxicology concerns (Table 1). I identified several chemicals in the fragrance mixture used by J&J in the talcum products with studies, in vitro and in vivo, published in peer reviewed journals demonstrating carcinogenicity, developmental or reproductive toxicity, genotoxicity, and or mutagenicity.

Four chemicals in Johnson's Baby Powder product have been identified by the International Agency for Research on Cancer (IARC) as potential carcinogens. "Benzene, ethenyl-", also known as Styrene [1], has been implicated as reproductive toxicant, neurotoxicant, and has been demonstrated to be a carcinogen in vivo and in vitro. Styrene is listed as such by several governmental and regulatory bodies (RTECS, Prop 65 among others). The National Toxicology Program considers styrene to be "reasonably anticipated to be a human carcinogen" (The National Toxicology Program (NTP), 2016). The FDA recently delisted Styrene from the Code of Federal Regulations as a food additive because FDA believed its use had been abandoned.

In addition, the U.S. Environmental Protection Agency considers p-cresol (also known as 4-methylphenol) to be "possibly carcinogenic"(U.S. Environmental Protection Agency, 1990). The International Agency for Research on Cancer (IARC) has stated that coumarin, eugenol, and d-limonene are "not classifiable" as to their carcinogenicity (Group 3). The remainder of the fragrance chemicals in the Baby Powder talcum product have not been evaluated by IARC as to their carcinogenicity.

Three fragrance chemicals added to J&J's Shower to Shower talcum product are included in the IARC monographs as possible carcinogens. Benzophenone has been classified by IARC as a Group 2B possible human carcinogen (International Agency for Research on Cancer (IARC), 2013b). Coumarin and eugenol are "not classifiable" as to their carcinogenicity (Group 3). In addition, Musk ketone is suspected of being a carcinogen, and has been classified as a Category 3 carcinogen by the Scientific Committee on Health and Environmental Risks (SCHER) in Europe. The remainder of the fragrance chemicals in the Shower to Shower product have not been evaluated by IARC as to their carcinogenicity.

Table 1 **Number of Fragrance Chemicals Added to Johnson & Johnson Talcum Products With Regulatory, Safety and Toxicology Concerns (Percent of Total Fragrance Chemicals Present)**

Category	Baby Powder	Shower to Shower
Regulatory Concerns	22 (15.6%)	20 (37.7%)
Safety /Toxicology Concerns	35 (24.8%)	12 (20.8%)

The fragrance chemicals were reviewed to identify those that are classified as irritants, skin irritants and eye irritants according to the Globally Harmonized System of Classification and Labelling of Chemicals in accordance with 29 CFR 1910 (OSHA HCS). More than 40% of the chemicals present in the fragrance mixture used by J&J in the talcum products are classified as irritants, greater than 70% are skin and eye irritants, and about 25% are sensitizers or allergens (Table 2).

Most of these fragrances were granted approval for cosmetic use based upon single administration dermal studies (i.e. the fragrance is applied to an animal once and examined for 24 hours). Few of the fragrance chemicals have been investigated with a Human Repeat Insult Patch Test (HRIPT), a study with repeat administration to the skin (i.e. daily administration for 1 week). In 2008, the fragrance industry recognized this shortcoming and is re-examining fragrance chemicals to identify issues and verify safe levels of exposure (Api et al., 2008).

Some fragrances were identified as eye irritants because the eye is a mucous membrane, as is the vagina. Fragrance chemicals that irritate the eye are also likely to irritate the vaginal mucosa.

[1] Styrene was replaced by Styrax Oil in April, 2014 according to Exhibit 3 "CHANGES TO JOHNSON'S BABY POWDER FRAGRANCE INGREDIENTS"

Table 2 **Number of Fragrance Chemicals Added to Johnson & Johnson Talcum Products Classified as Irritants, Sensitizers and Allergens (Percent of Total Fragrance Chemicals Present)**

Category	Baby Powder	Shower to Shower
Irritants	58 (41.1%)	25 (47.2%)
Skin Irritants	110 (78.0%)	44 (83.0%)
Eye Irritants	104 (73.8%)	40 (75.5%)
Sensitizers	39 (27.7%)	16 (30.2%)
Allergens	35 (24.8%)	16 (30.2%)

The International Fragrance Association (IFRA) is the official self-regulatory representative body of the fragrance industry worldwide. IFRA's main purpose is to ensure the safety of fragrance materials through a dedicated science program and publishes a list of usage standards for fragrance materials, limiting or prohibiting the use of ingredients, based on the findings of the Research Institute of Fragrance Materials (RIFM). RIFM gathers data regarding the safety of fragrance materials.

The fragrance chemicals were reviewed to identify those that are classified with IFRA Critical Effects, limitations for baby powder and talcum products (a Category 5 Limitation) and dermal exposure limits. More than 25% of the chemicals present in the fragrance mixture used by J&J in the talcum products have an IFRA Critical Effect, and greater than 15% have exposure limitations in baby powder and talcum products (Table 3).

Table 3 **Number of Fragrance Chemicals Added to Johnson & Johnson Talcum Products with IFRA Critical Effects and Exposure Limitations (Percent of Total Fragrance Chemicals Present)**

Category	Baby Powder	Shower to Shower
IFRA Critical Effects	39 (27.7%)	15 (28.3%)
IFRA Category 5 Limits	23 (16.3%)	13 (24.5%)
IFRA Exposure Limits	25 (17.7%)	9 (17.0%)

The fragrance chemicals were reviewed to identify those listed on the Inactive Ingredient Database (IID) maintained by the US Food and Drug Administration. The IID provides information on inactive ingredients present in FDA-approved drug products. The inactive ingredients on this list have been subject to extensive toxicology studies for a given route of administration (i.e. oral, injected or vaginal).

About 20% of the chemicals present in the fragrance mixture used by J&J in the talcum products are listed on the IID, about 11% are present in an approved drug product for topical administration to the skin, and less than 4% are present in an approved drug product for vaginal administration (Table 4).

Table 4 **Number of Fragrance Chemicals Added to Johnson & Johnson Talcum Products Listed on the FDA IID (Percent of Total Fragrance Chemicals Present)**

Category	Baby Powder	Shower to Shower
IID Listed	26 (18%)	11 (21%)
IID Listed for Topical Administration	9 (6%)	6 (11%)
IID Listed for Vaginal Administration	1 (1%)	2 (4%)

FDA and EFSA consider oral administration for flavors. IFRA and CIR consider topical administration (i.e. application to the skin) for fragrances and cosmetic ingredients. In this matter, the talcum products were applied to the perineal area. The transport of talcum products into the vaginal cavity and exposure to the vagina, endometrium, fallopian tubes, and ovaries would be an unintended consequence of perineal application of these products. The safety margins of the 175 fragrance chemicals were determined for foods (oral administration) or cosmetics (topical application to the skin), except for the three fragrance chemicals listed on the FDA IID present in an approved drug product administered to the vagina. In other words, only three of the 175 fragrance chemicals have been investigated for safety in the vagina. The fragrances that are irritants (particularly mucosal irritants), sensitizers and allergens can cause inflammation and oxidative stress. Accordingly, in my opinion, the fragrance chemicals in the Johnson & Johnson talcum powder products contribute to the inflammatory properties, toxicity, and potential carcinogenicity of these products.

2 QUALIFICATIONS

I earned a B.S. in Chemistry from the University of Missouri–St. Louis, an M.A. in Organic Chemistry from Washington University in St. Louis and a Ph.D. in Molecular Pharmaceutics from the University of Texas.

I am currently the President of Theridian Technologies, LLC, a pharmaceutical development consulting firm established in March 2009. I have served as a consultant to more than 50 companies, mostly in the pharmaceutical industry. I primarily consult in the area of proof of concept, formulation and product development, drug delivery and clinical development, including generation of FDA regulatory submissions.

In 2015, I co-founded Oticara, Inc., a startup pharmaceutical company developing novel drug products for the treatment for infectious disease. I also serve on the Board of Directors for Texas EnteroSorbents, a life science company.

From 2003 to 2009, I was an owner (Member) and employed by PharmaForm, LLC, a contract research organization providing formulation and drug product development services. I served as Vice President, Business Development; Vice President, Quality Control and Analytical Services; and Vice President, Drug Delivery Technology & Manufacturing. From 1995 until 2000, I worked in research and development at Mission Pharmacal Company in San Antonio, Texas. From 1992 to 1995, I worked as a chemist at Warner-Jenkinson Company in St. Louis, Missouri. In these roles, I worked on the development of pharmaceutical formulations, nutritional supplements and food products.

During my career, I have developed over 50 formulations that have been tested in human clinical studies. I have authored or co-authored over 15 clinical study protocols, including the pharmacy manual, daily diary, investigators brochure, informed consent form, adverse event tracking log, and drug dispensation log. I have been present in the clinic when participants have been dosed and have audited clinical study sites.

I have authored or co-authored over 30 published articles and abstracts and four book chapters relating to my work. Among my publications are a significant number of articles concerning pharmaceutical formulation techniques in general, and the effects of certain formulation techniques and excipients. I also am an inventor on five United States patents as well as a number of foreign patents and pending applications relating to my work.

One of my articles, "Pharmaceutical Applications of Hot-Melt Extrusion: Part I" published in Drug *Development and Industrial Pharmacy* in 2007, was the most downloaded manuscript from the publisher in 2011 and 2012.

I have served as a reviewer for many peer reviewed journals, including the *Journal of Pharmaceutical Sciences, Drug Development and Industrial Pharmacy, European Journal of Pharmaceutics and Biopharmaceutics, Journal of Pharmacy and Pharmacology, European Journal of Pharmaceutics, Pharmaceutical Research, International Journal of Pharmaceutics, Journal of Microencapsulation, S.T.P. Pharma Sciences (France), Pharmaceutical Development and Technology, Journal of Controlled Release*, and *AAPS PharmSciTech.*

My current research focuses on the formulation, development, optimization, and delivery of small organic compounds, peptides and proteins by a variety of technologies, including hot melt extrusion and thermal processing techniques, depot drug delivery, oral drug delivery, pulmonary drug delivery, implantable drug delivery and abuse deterrent drug delivery.

In the last five years, I have testified as an expert by deposition in the following cases:

- *Grünenthal, GmbH et al. v. Teva Canada Ltd. et al.*, Court File No. T-1009-14 (Can. Fed. Ct.).
- *In Re CIPRODEX*, Consolidated Civil Action No. 3:15-cv-05756 (PGS) (DEA) (D.N.J.).

A copy of my curriculum vitae is attached as Appendix C to this Report. I am being compensated for my work at a rate of $600 per hour.

3 SOURCES CONSIDERED

A List of sources considered during generation of this report is provided in Table 5. References from the scientific literature are provided in Section 7.

Table 5 Sources Considered

Source	Link / Background
Canadian Cosmetic Ingredient Hotlist: Prohibited and Restricted Ingredients	https://www.canada.ca/en/health-canada/services/consumer-product-safety/cosmetics/cosmetic-ingredient-hotlist-prohibited-restricted-ingredients/hotlist.html
Cell Proliferation	https://onlinelibrary.wiley.com/journal/13652184
CFR - Code of Federal Regulations Title 21	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm
ChemSec SIN List	http://chemsec.org/sin-list/
ChemSpider	http://www.chemspider.com/

Source	Link / Background
Cosmetic Ingredient Review	https://www.cir-safety.org/ingredients
Educational report of Dr. Thomas Dydek, PhD, DABT, PE regarding the cancer-causing constituents of defendants' talcum powder products	
The EFSA Journal (The European Food Safety Authority Journal)	https://efsa.onlinelibrary.wiley.com/journal/18314732
Environmental and Molecular Mutagenesis	https://onlinelibrary.wiley.com/journal/10982280
EU Annex ii: Chemicals prohibited from cosmetics in the EU	http://ec.europa.eu/growth/tools-databases/cosing/pdf/COSING_Annex%20II_v2.pdf
European Union Endocrine Disruptors Priority List	http://ec.europa.eu/environment/chemicals/endocrine/strategy/substances_en.htm
Evaluation Of Certain Food Additives And Contaminants, WHO Technical Report Series, Fifty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives, World Health Organization Geneva, 2002	http://www.who.int/foodsafety/publications/monographs/en/
EPA Distributed Structure-Searchable Toxicity (DSSTox) Database	https://www.epa.gov/chemical-research/distributed-structure-searchable-toxicity-dsstox-database
FDA Inactive Ingredient Search for Approved Drug Products	https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm
FDA The Substances Added to Food Inventory	https://www.accessdata.fda.gov/scripts/fdcc/?set=FoodSubstances
FDA Substance Registration System	https://fdasis.nlm.nih.gov/srs/
FEMA	https://www.femaflavor.org/
FEMA Flavor Ingredient Library	https://www.femaflavor.org/flavor-library
Food and Chemical Toxicology	https://www.journals.elsevier.com/food-and-chemical-toxicology
The Food and Agriculture Organization (FAO) of the United Nations Online Edition: "Specifications for Flavourings"	http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-flav/en/
The Good Scents Company Information System	http://www.thegoodscentscompany.com/index.html
International Journal of Toxicology	http://journals.sagepub.com/home/ijt
IFRA	http://www.ifraorg.org/
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JNJTALC000113055	
JNJTALC000126887	
JNJTALC000383896	
PCPC_MDL00012948	
PROTECTED - Powder Fragrance Ingredients	Supplemental Answer to Plaintiffs' Second Set of Interrogatories No. 19, Ingham, et al., v. Johnson & Johnson, et al Attorney Eyes Only Documents (Exhibit 1, Exhibit 2, and Exhibit 3)
Monographs on Fragrance Raw Materials A Collection of Monographs originally appearing in Food and Cosmetics Toxicology An International Journal, Edited by D. L. J. Opdyke. Pergamon Press New York 1979 eBook ISBN: 9781483147970	https://www.elsevier.com/books/monographs-on-fragrance-raw-materials/opdyke/978-0-08-023775-6
National Library of Medicine Drug Information Portal	https://druginfo.nlm.nih.gov/drugportal/
Personal Care Products Council (formerly CTFA)	https://www.personalcarecouncil.org/
PubChem	https://pubchem.ncbi.nlm.nih.gov/
Regulatory Toxicology and Pharmacology	https://www.journals.elsevier.com/regulatory-toxicology-and-pharmacology
Research Institute for Fragrance Materials (RIFM)	https://www.rifm.org/
Registry of Toxic Effects of Chemical Substances (RTECS)	https://www.cdc.gov/niosh/rtecs/default.html
ToxNet	https://toxnet.nlm.nih.gov/
Women's Voices for the Earth (WVE)	https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/

4 FRAGRANCE CHEMICALS IN JOHNSON & JOHNSON BABY POWDER PRODUCT

The Johnson & Johnson Baby Powder product contains 141 fragrance chemicals. Some of these fragrances are themselves a mixture of chemicals.

4.1 Unidentified Fragrance Chemicals

One fragrance chemical could not be identified: Caprylyl Alcohol. A Google search did not return definitive information to enable identification. It is likely a typographical error in the above document,

and it is likely meant to be Caprylic Alcohol, which is a known fragrance. This fragrance chemical is not included in the analysis below since it cannot be identified definitively.

4.2 Fragrance Chemical Regulatory Review

In the U.S., manufacturers of consumer products, and owners of chemical formulations (such as fragrances) in those products, are not required to disclose all ingredients to consumers (Steinemann, 2009). The product label for fragranced products regulated under the Federal Food, Drug, and Cosmetic Act ("FFDCA") needs to list the word "fragrance," but not the ingredients in the fragrance (21 C.F.R. Section 701.3). The label may also list a similar term, such as "perfume," "parfum," "natural fragrance," "pure fragrance," "organic fragrance," etc., although those terms do not have a legal definition.

Regulation of consumer products largely falls under the Consumer Product Safety Act ("CPSA"). The CPSA does not require disclosure of all ingredients in products. Instead of listing ingredients, a manufacturer can provide other information on a product, such as a warning label. Similarly, the Federal Hazardous Substances Act (FHSA) requires warning labels for hazardous substances, but does not require that all ingredients be disclosed on the product's label. Ingredients can also be exempt from disclosure through "trade secrets" protection. Under the FFDCA, fragrance ingredients that qualify as trade secrets may be listed as "and other ingredients" without disclosing the ingredients.

The Toxic Substances Control Act (TSCA) of 1976 authorizes the EPA to secure information on all new and existing chemicals (or mixtures) sold in interstate commerce.

A regulatory review of the fragrance chemicals was performed. Twenty-three (23) fragrance chemicals in the Johnson & Johnson Baby Powder product were identified that are either (1) not listed in Title 21 of the Code of Federal Regulations, (2) not approved for fragrance of flavor use, (3) not permitted for cosmetic use, (4) requires warnings, (5) are not permitted for use on the body (6) absence of an IFRA Standard (7) absence of a CIR listing, or a CIR listing as unsafe or insufficient data to support safety.

A summary of the fragrance chemicals with regulatory concerns is provided in Table 6. A comparison of the number of fragrance chemicals with regulatory concerns to the total number of fragrance chemicals is provided in Figure 1.

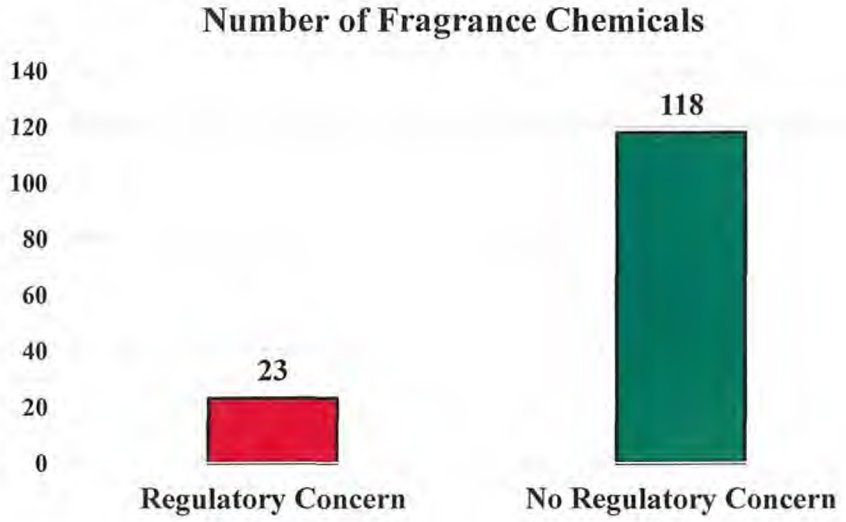
Table 6 Fragrance Chemicals Added to Johnson & Johnson Baby Powder Product with Regulatory Concerns

Fragrance Chemical	Regulatory Concern
1-Cedr-8-en-9-ylethanone	Not listed in CFR Title 21 No IFRA Standard Not listed by CIR
2-Propanol, 1,1'-oxybis-	Not for Fragrance or Flavor Use No IFRA Standard
3-(5,5,6-Trimethylbicyclo[2,2,1]hept-2-yl)cyclohexanol	Not listed in CFR Title 21 No IFRA Standard Not Listed by CIR
3-Methyl-5-(2,2,3-trimethylcyclopent-3-en-1-yl)pentan-2-ol	Not listed in CFR Title 21 No IFRA Standard Not Listed by CIR

Fragrance Chemical	Regulatory Concern
8-Cyclohexadecen-1-one	Not listed in CFR Title 21 No IFRA Standard Not listed by CIR
Benzene, ethenyl-	Not for Fragrance or Flavor Use No IFRA Standard Not listed by CIR
Benzoic acid, 2,4-dihydroxy-3,6-dimethyl-, methyl ester	Not listed in CFR Title 21 No IFRA Standard Not listed by CIR
Cedrol	Not listed in CFR Title 21 No IFRA Standard Not listed by CIR
Cedrus Atlantica (Cedarwood) Bark Oil	Not listed in CFR Title 21 No IFRA Standard Not Listed by CIR
Citrus Medica Limonum (Lemon) Peel Oil	TSCA Do Not Use on Skin No IFRA Standard Not Listed by CIR
Copper Chlorophyll	Colorant, Not a fragrance No longer allowed for cosmetic use Not listed by CIR
Coumarin	Prohibited in foods (banned in 1954) Not listed by CIR
Hex-3-en-1-yl acetate	Not listed in CFR Title 21 No IFRA Standard Not listed by CIR
Hexamethylindanopyran	Not listed in CFR Title 21 No IFRA Standard Not listed by CIR
Mentha Arvensis Leaf Oil	Not listed in CFR Title 21 No IFRA Standard Not listed by CIR
Methyl 2-(methylamino)benzoate	Requires nitrosamine warning Not listed by CIR
Methyl Hydrogenated Rosinate	Not a Fragrance No IFRA Standard Not listed by CIR
Myroxylon Pereirae (Balsam Peru) Oil	Prohibited as Fragrance Chemical; Do not use on any part of the body IFRA Prohibited Fragrance Chemicals on the EU Annex ii: Chemicals prohibited from cosmetics in the EU Not listed by CIR
p-Cresol	Not permitted in cosmetics Cosmetic Ingredient Review (CIR): rated "Z": the available data are insufficient to support safety

Fragrance Chemical	Regulatory Concern
Phenoxyethanol	Approved for Indirect Food Contact No IFRA Standard
Santalum Album (Sandalwood) Oil	Only certain types allowed for fragrance use No IFRA Standard Not listed by CIR
Tartaric Acid	Not a fragrance Not for Fragrance Use No IFRA Standard Not listed by CIR

Figure 1 Fragrance Chemicals with Regulatory Concerns



4.3 Fragrance Chemical Safety and Toxicology Review

The RIFM Expert Panel ("REXPAN") examines the dermal effects, systemic toxicity and environmental consequences of the use of and exposure to fragrance materials (D. R. Bickers et al., 2003). The REXPAN approach involves grouping more than 2,600 discrete ingredients into classes, based on chemical structures. Research sponsored by RIFM, data supplied by member companies, and relevant published reports from many sources are considered during hazard characterization. This process results in well-documented conclusions which are provided to the International Fragrance Association (IFRA) as the basis for consideration of a new or existing Fragrance Material Standard. The RIFM's methods are modeled after the National Academy of Sciences' (NRC) Elements of Risk Assessment and Risk Management (National Research Council Committee on Risk Assessment of Hazardous Air, 1994).

The Cosmetic Ingredient Review was established in 1976 by the industry trade association (then the Cosmetic, Toiletry, and Fragrance Association, now the Personal Care Products Council (PCPC). PCPC funds the CIR, and CIR does not usually review fragrances, colors, or flavorings.

The fragrance chemicals in Johnson's Baby Powder Product were reviewed for safety and toxicology. Thirty-five (35) fragrance chemicals were found to be listed on the RTECS list (Registry of Toxic Effects of Chemical Substances maintained by the Center for Disease Control) or had safety in use concerns.

Four chemicals in Johnson's Baby Powder product have been identified by the International Agency for Research on Cancer (IARC) as potential carcinogens. "Benzene, ethenyl-", also known as Styrene, has been implicated as reproductive toxicant, neurotoxicant, and has been demonstrated to be a carcinogen in vivo and in vitro. It is my understanding that Styrene was removed from Johnson's Baby Powder in April, 2014. Styrene is listed as such by several governmental and regulatory bodies (RTECS, Prop 65 among others). The National Toxicology Program considers styrene to be "reasonably anticipated to be a human carcinogen" (The National Toxicology Program (NTP), 2016). The FDA recently delisted Styrene from the Code of Federal Regulations as a food additive because FDA believed its use had been abandoned.

In addition, the U.S. Environmental Protection Agency considers p-cresol (also known as 4-methylphenol) to be "possibly carcinogenic" (U.S. Environmental Protection Agency, 1990). The International Agency for Research on Cancer (IARC) has stated that coumarin, eugenol, and d-limonene are "not classifiable" as to their carcinogenicity (Group 3). The remainder of the fragrance chemicals in Baby Powder have not been evaluated by IARC as to their carcinogenicity.

Styrene was recently removed from use in foods by FDA (U.S. Food and Drug Administration, 2018). Notably, the FDA noted that use of Styrene as a synthetic flavoring substance and adjutant in food has been abandoned.

Several chemicals in the fragrance mixture used by J&J in the talcum products were identified with in vitro and in vivo studies published in peer reviewed journals demonstrating carcinogenicity, developmental or reproductive toxicity, genotoxicity, and or mutagenicity. While these studies are not definitive that the same effects would be observed in humans, they are indicators of biological activity.

For example, The European Food Safety Authority concluded that Ethyl 3-methyl-3-phenyloxirane-2-carboxylate, also known as Ethyl Methylphenylglycidate, "there is substantial evidence of a genotoxic potential from the available in vitro and in vivo studies (European Food Safety Authority, 2009).

The CIR Expert Panel concluded there is insufficient information available to support the safety of Juniperus Communis Fruit Oil for use in cosmetics (Cosmetic Ingredient Review Expert Panel, 2001b).

Similarly, the CIR Expert Panel found that p-Cresol was considered positive for inducing chromosomal aberrations in CHO cells under both activation and nonactivation conditions, and the available data are insufficient to support the safety in cosmetics (Cosmetic Ingredient Review Expert Panel, 2006). Boutwell and Bosch reported that p-Cresol was co-carcinogenic and promoted tumors on mouse skin (Boutwell & Bosch, 1959).

A summary of the findings is provided in Table 7 and a comparison of the number of fragrance chemicals with safety and toxicology concerns to the total number of fragrance chemicals in the product is provided in Figure 2.

Table 7 Fragrance Chemicals Added to Johnson & Johnson Baby Powder Product on the RTECS List and or Toxicity Concerns

Fragrance Chemical	RTECS	Toxicity Concern
(d)-Limonene	x	Reproductive Effects in mice and rats following oral administration (RTECS). Cytotoxicity in vitro Chinese Hamster Ovary cells IC_{50} > 50 µg/mL (Kpoviessi et al., 2014) IARC potential carcinogen: "There is inadequate evidence in humans for the carcinogenicity of d-limonene. There is sufficient evidence in experimental animals for the carcinogenicity of d-limonene." (International Agency for Research on Cancer (IARC), 1999)
1,2-Dimethoxy-4-prop-l-en-1-ylbenzene	x	
2-Propanol, 1,1'-oxybis-	x	
3-Methyl-1H-indole "Skatole"	x	Mutagenic and a possible pulmonary carcinogen (RTECS) Cytotoxic in Chinese Hamster Ovary cells at 1.3 and 1.4 mmol/L in 3 hours. DNA Adduct (could be carcinogenesis) in Chinese Hamster Ovary cells at 1.3 and 1.6 mmol/L in 3 hours. DNA Inhibition in Chinese Hamster Ovary model at 1.3 mmol/L in 3 hours (Reddy et al., 2002).
3-Methyl-5-(2,2,3-trimethylcyclopent-3-en-1-yl)pentan-2-ol		Listed in Toxic Substances Control Act (TSCA) Chemical Substance Inventory
4-(2,6,6-Trimethylcyclohex-2-en-1-yl)but-3-en-2-one		At 25 mM concentration caused significant increases in chromosome aberrations. No reproductive and developmental tox available, and no carcinogenicity data available. (J. Lalko et al., 2007)
4-Methylphenyl 2-methylpropanoate	x	
Acetic acid, phenylmethyl ester	x	
Benzaldehyde	x	It was positive in sister chromatid exchange assay with human lymphocytes from healthy non-smoking donors. Benzaldehyde was found to induce formation of stable DNA-protein cross-links in cultured human lymphoma cells. (TOXNET) May have a significant genotoxic effects.(Demir, Kocaoğlu, & Kaya, 2008) Cytogenic at 50 nmol/L/24H in Chinese Hamster Ovary cells (RTECS) Sister chromatid exchange (mutation) in Chinese Hamster Ovary cells (Galloway et al., 1987).
Benzaldehyde, 2-hydroxy-		H341: Suspected of causing genetic defects (germ cell mutagenicity)
Benzene, ethenyl-	x	Styrene has been implicated as reproductive toxicant, neurotoxicant, or carcinogen in vivo or in vitro (*Sax's Dangerous Properties of Industrial Materials*, 2004). FDA filed a food additive petition (FAP 6A4817) proposing that to amend § 172.515 to no longer provide for the use of styrene as a synthetic flavoring

Fragrance Chemical	RTECS	Toxicity Concern
		substance and adjuvant in food because the use has been abandoned. FDA published a final rule granting the petition to no longer authorize the use of styrene as a synthetic flavoring substance and adjuvant in food because its use under § 172.515 has been permanently and completely abandoned. Styrene, it has been observed, crosses the placenta (*Sax's Dangerous Properties of Industrial Materials*, 2004). Prop 65 List of Carcinogens Agency for Toxic Substances and Disease Registry Styrene is possibly carcinogenic to humans (Group 2B) (International Agency for Research on Cancer (IARC), 2002) Styrene 7,8-oxide, the metabolite of styrene, and a monofunctional alkylating agent, has given positive results in virtually every short-term genetic assay in vitro and, to a lesser degree, in vivo. Positive results have previously been reported for gene mutations in bacteria and mammalian cells in vitro. DNA strand breaks, alkali-labile sites, and cytogenetic damage also have been reported in mammalian cells in vitro and, to some degree, in vivo.(International Agency for Research on Cancer (IARC), 2002) Cytogenic, DNA Damage, DNA Inhibition, Sister Chromatid Exchange, Unscheduled DNA Synthesis in multiple in vitro models (RTECS).
Benzeneacetic acid	x	Reproductive Toxicity in rats (RTECS).
Benzyl Alcohol	x	Cytogenetic in Chinese Hamster Ovary cells at 4 µg/L dose (National Toxicology Program, 1989) Acceptable daily intakes were established by the World Health Organization at 5 mg/kg for Benzyl Alcohol. Benzyl Alcohol could be used safely at concentrations up to 5%, but that manufacturers should consider the non-immunologic phenomena when using benzyl alcohol in cosmetic formulations designed for infants and children. (Cosmetic Ingredient Review Expert Panel, 2001a)
Benzyl Benzoate	x	
Benzyl Salicylate	x	BzS showed obvious in vitro hERα agonistic activities; BzS in particular exhibited a higher estrogenic activity compared to bisphenol A (BPA) (Zhang et al., 2012).
Camphor	x	Restricted from fragrance use in Canada
Caproic Acid	x	Developmental or Reproductive Toxicity: Caproic acid caused microencephaly and other abnormalities in frog embryos. (*Patty's Toxicology*, 2001)
Citral	x	Selective oocyte degeneration and impaired fertility following dermal application to female rats (Toaff, Abramovici, Sporn, & Liban, 1979) Reproductive Effects in rats at 85 ppm inhaled dose (RTECS)

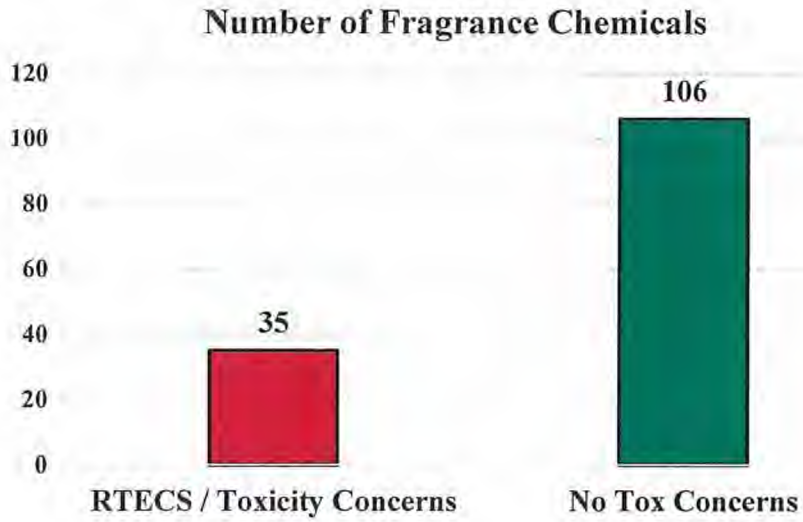
Fragrance Chemical	RTECS	Toxicity Concern
		Valid genotoxicity (induction of sister chromatid exchange) result in Chinese hamster ovary cells at 0.289–8.86 µg/mL dose (National Toxicology Program (NTP), 2003) Cytogenetic in vitro result in Chinese Hamster Ovary cell IC_{50} = 20.6 µg/mL (Kpoviessi et al., 2014)
Coumarin	x	Recent evidence indicates coumarin causes liver tumors in rats and mice and Clara cell toxicity and lung tumors in mice (Wishart, 2018). Reproductive: Effects on embryo or fetus: Fetotoxicity (except death, e.g., stunted fetus) in rats (RTECS) Sister chromatid exchange (mutation) in Chinese Hamster Ovary cells (Galloway et al., 1987). IARC potential carcinogen (International Agency for Research on Cancer (IARC), 2000) Sister chromatid exchange (mutation) and chromosomal abberrations in Chinese Hamster Ovary cells (National Toxicology Program (NTP), 1993)
Dimethylhydroquinone	x	Chronic neurotoxic effects include vision disturbances (O'Donoghue, 1985)
Ethyl 3-methyl-3-phenyloxirane-2-carboxylate "Ethyl Methylphenylglycidate"		Sister Chromatid Exchange and Chromosome Aberration in Chinese Hamster Ovary Cells (16 – 160 µg/mL) (Galloway et al., 1987) "There is substantial evidence of a genotoxic potential from the available in vitro and in vivo studies. (European Food Safety Authority, 2009)
Eugenol		IARC potential carcinogen (Group 3 "not classifiable") (International Agency for Research on Cancer (IARC), 1985) Sister Chromatid Exchange (11 – 123 µg/mL) and Chromosome Aberration in Chinese Hamster Ovary Cells (198 – 300 µg/mL) (Galloway et al., 1987).
Isoamyl Acetate	x	Central nervous depressant (Gosselin, Smith, & Hodge, 1984)
Juniperus Communis Fruit Oil		Juniperus Communis Extract did affect fertility and was abortifacient in studies using albino rats, but was not teratogenic. (Cosmetic Ingredient Review Expert Panel, 2001b) … dermal reproductive/developmental toxicity data (to include determination of a no-effect level); two genotoxicity assays (one in a mammalian system) for each extract; if positive, a 2-year dermal carcinogenicity assay performed using National Toxicology Program (NTP) methods is needed; a 2-year dermal carcinogenicity assay performed using NTP methods on Juniperus Oxycedrus Tar; and irritation and sensitization data on each extract and the tar (these data are needed because the available data on the oils cannot be extrapolated). Until these data are

Fragrance Chemical	RTECS	Toxicity Concern
		available, it is concluded that the available data are insufficient to support the safety of these ingredients in cosmetic formulations. (Cosmetic Ingredient Review Expert Panel, 2001b)
Lavandula Angustifolia (Lavender) Oil		This study has demonstrated that lavender oil is cytotoxic to human skin cells in vitro (endothelial cells and fibroblasts) at a concentration of 0.25% (v/v) in all cell types tested (HMEC-1, HNDF and 153BR) (Prashar, Locke, & Evans, 2004).
Linalool	x	Reproductive Effects (RTECS) Linalool was found to be moderately cytotoxic to Chang, HeLa, and KB cells (C Nachev, Zolotovitch, Siljanovska, & Stojcev, 1967). When tested against HeLa cells in monolayer culture, linalool was cytotoxic at 100 ug/L, weakly active at 10 ug/L, and inactive at 1 ug/L (CH Nachev, Zolotovitch, Siljanowska, & Stojcev, 1968)
Linalyl Acetate	x	"Linalyl acetate induced a significant increase of MN frequency; the maximum chromosomal damage, observed at 100 µg/ml, was up to fourfold higher than the corresponding control value. The effect was concentration dependent and a significant concentration–response relationship was detected" (Di Sotto, Mazzanti, Carbone, Hrelia, & Maffei, 2011) "The genotoxicity of linalyl acetate described here in mammalian cells strengthens the data obtained in the bacterial ones and highlights the need of in vivo studies." (Di Sotto et al., 2011) Linalyl acetate showed weak cocarcinogenic activity (van Duuren et al., 1971).
Methyl Benzoate	x	"Methyl benzoate was cytotoxic to HeLa cells at 683.30 mmol/L, A flavus at 2.5 mg/mL, A parasiticus at 5.0 mg/mL, and lung fibroblasts at 25 mmol/L." "Not only caused toxic effects to the cells but also promoted membrane penetration by other substances" (Becker et al., 2012).
Methyl Salicylate	x	
Oils, styrax	x	Sister chromatid exchange (mutation) in Chinese Hamster Ovary observed (Gulati, Witt, Anderson, Zeiger, & Shelby, 1989).
p-Cresol	x	Cytogenetic in Chinese Hamster Ovary cells, DNA Damage in human lymphocytes, and morphologic transformation in mouse fibroblast (RTECS) "In the p-Cresol assay without metabolic activation, there were significant increases in chromosomal aberrations at all concentrations tested (100 to 300 µg/ml)." (Cosmetic Ingredient Review Expert Panel, 2006) "p-Cresol was considered positive for inducing chromosomal aberrations in CHO cells under both activation and nonactivation conditions" (Cosmetic Ingredient Review Expert Panel, 2006)

Fragrance Chemical	RTECS	Toxicity Concern
		"Cresol and Thymol are not permitted for use in cosmetics that are applied on mucous membranes (except Thymol when limited to the mouth). (Cosmetic Ingredient Review Expert Panel, 2006) "p-Cresol is demonstrated to cause depigmentation of hair and possibly the skin. In addition, there is concern that p-Cresol may be a strong allergen. There was insufficient data for the Panel to determine a safe use level that would not sensitize or produce chemical leukoderma for p-Cresol and Mixed Cresols (which contains p-Cresol). Therefore, the Panel considered that the available data are insufficient to support the safety of these two ingredients in cosmetics. Studies are needed which would demonstrate no chemical leukoderma at concentrations of use of p-Cresol and Mixed Cresols, or would demonstrate a dose response from which a safe concentration could be derived." (Cosmetic Ingredient Review Expert Panel, 2006). Co-carcinogenic following dermal application to mice. (Boutwell & Bosch, 1959) "Classification: C; possible human carcinogen. Basis For Classification: Based on an increased incidence of skin papillomas in mice in an initiation-promotion study. The three cresol isomers produced positive results in genetic toxicity studies both alone and in combination. Human Carcinogenicity Data: Inadequate. Animal Carcinogenicity Data: Limited." (U.S. Environmental Protection Agency, 1990) Cosmetic Ingredient Review: Rated "Z": the available data are insufficient to support safety https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr277.pdf Women exposed in their workplace (enamel-insulated wire manufacturing) to varnishes that contained Mixed Cresols (amount not stated) had increased gynecological problems such as menstrual disorders and hormonal disturbances. An increased frequency of perinatal mortality and abnormal development of newborn infants was also reported Syrowadko and Malysheva (1977) (Syrowadko & Malysheva, 1977) Agency for Toxic Substances and Disease Registry
p-Cymene	x	Cytotoxicity in vitro Chinese Hamster Ovary cells IC_{50} > 50 µg/mL (Kpoviessi et al., 2014)
Phenethyl Alcohol	x	Mutation and Reproductive Effects (RTECS)
Phenoxyethanol	x	Mutation and Reproductive Effects (RTECS) "Dermal exposure to these compounds can result in localized or systemic toxicity including skin sensitization and irritancy, reproductive, developmental and hematological effects." (Lockley, Howes, & Williams, 2005)
Propanedioic acid, diethyl ester	x	Tumorigenic in mice following oral dosing (RTECS)

Fragrance Chemical	RTECS	Toxicity Concern
Vanillin	x	

Figure 2 Fragrance Chemicals with Toxicity Concerns



4.4 Fragrance Chemicals Classified As Irritants

A stimulus or agent which induces the state of irritation is designated an "irritant". In biology and physiology, irritation is a state of inflammation or a painful reaction to allergy or cell-lining damage.

The fragrance chemicals were reviewed to identify those that are classified as irritants ("Xi"), skin irritants and eye irritants according to the Globally Harmonized System of Classification and Labelling of Chemicals in accordance with 29 CFR 1910 (OSHA HCS).

The "Xi" designation is used on Material Safety and Data Sheets (MSDS) for non-corrosive substances and preparations which, through immediate, prolonged or repeated contact with the skin or mucous membrane, may cause inflammation. Fragrance Chemicals with R36, H315 or equivalent designations were classified as skin irritants. Fragrance Chemicals with R38, H319 or equivalent designations were classified as eye irritants.

The eye is a mucous membrane. A mucous membrane or mucosa is a membrane that lines various cavities in the body and covers the surface of internal organs. It consists of one or more layers of epithelial cells overlying a layer of loose connective tissue. It is mostly of endodermal origin and is continuous with the skin at various body openings such as the eyes, ears, inside the nose, inside the mouth, lip, vagina, the urethral opening, and the anus. Some mucous membranes secrete mucus, a thick protective fluid. The function of the membrane is to stop pathogens and dirt from entering the body and to prevent bodily tissues from becoming dehydrated.

Of the 141 fragrance chemicals in the product, 58 fragrance chemicals are designated as irritants, 110 are designated as skin irritants and 104 are eye irritants.

A summary of the findings is provided in Table 8 and a comparison of the number of fragrance chemicals designated as irritants, skin irritants and eye irritants are provided in Figure 3, Figure 4, and Figure 5.

Table 8 Fragrance Chemicals Added to Johnson & Johnson Baby Powder Product Listed as Irritants, Skin Irritants and Eye Irritants

Fragrance Chemical	Irritant	Skin Irritant	Eye Irritant
(d)-Limonene		x	x
1-(2,6,6-Trimethylcyclohex-2-en-1-yl)pent-1-en3-one		x	
1,2-Dimethoxy-4-prop-l-en-1-ylbenzene		x	x
1,5-Dimethyl-1-vinylhex-4-en-I-yl benzoate			x
1,7,7-Trimethylbicyclo[2,2,1]heptan-2-ol	x	x	x
1-acetonaphthone		x	x
1-Benzazole		x	x
1-Cedr-8-en-9-ylethanone		x	x
1-Methyl-1-(4-methylcyclohex-3-en-l-yl)ethyl acetate	x	x	x
2-Acetonaphthone		x	x
2-Isopropenyl-5-methylcyclohexanol		x	x
2-Isopropyl-5-methylcyclohexanol	x	x	x
2-Phenylethyl 3-methylbutanoate	x	x	x
2-Phenylethyl formate		x	x
2-Phenylethyl phenylacetate	x	x	x
2-Propanol, 1,1'-oxybis-		x	x
3-(5,5,6-Trimethylbicyclo[2,2,1]hept-2-yl)cyclohexanol		x	x
3,7-Dimethyloct-6-en-l-ol	x	x	x
3,7-Dimethylocta-2,6-dien-1-yl acetate	x	x	x
3,7-Dimethylocta-2,6-dien-1-yl benzoate		x	x
3-Methyl-1H-indole	x	x	x
3-Methyl-5-(2,2,3-trimethylcyclopent-3-en-1-yl)pentan-2-ol		x	x
3-Phenylpropan-1-ol	x	x	x
4-(2,6,6-Trimethylcyclohex-2-en-1-yl)but-3-en-2-one	x	x	x
4-Methylphenyl 2-methylpropanoate	x	x	x
4-Methylphenyl octanoate		x	x
5-Isopropenyl-2-methylcyclohex-2-en-1-one		x	
8-Cyclohexadecen-1-one		x	
Acetic acid, phenylmethyl ester	x	x	x
Aldehyde C-7		x	x
Alpha-Isomethyl Ionone		x	x
Amyl Cinnamal	x	x	x
Anisaldehyde	x	x	x
Benzaldehyde		x	x

Fragrance Chemical	Irritant	Skin Irritant	Eye Irritant
Benzaldehyde, 2-hydroxy-		x	x
Benzene, 1,3-dimethoxy-	x	x	x
Benzene, ethenyl-		x	x
Benzeneacetic acid	x	x	x
Benzeneacetic acid, methyl ester		x	x
Benzoic acid, 2,4-dihydroxy-3,6-dimethyl-, methyl ester	x	x	x
Benzoic acid, 2-hydroxy-, 2-methylpropyl ester		x	x
Benzoic acid, 2-hydroxy-, ethyl ester		x	x
Benzyl Alcohol		x	x
Benzyl Benzoate		x	x
Benzyl Salicylate		x	x
Boswellia Carterii Oil		x	x
Bulnesia sarmienti, ext.	x	x	
Butanoic acid, ethyl ester	x	x	x
Butanoic acid, pentyl ester	x	x	x
Camphor		x	x
Caproic Acid		x	x
Carum Carvi (Caraway) Fruit Oil	x	x	x
Cedrol	x	x	x
Cedrus Atlantica (Cedarwood) Bark Oil	x	x	x
Celery seed (Apium graveolens L.)	x		x
Cinnamal	x	x	x
Cinnamyl Alcohol	x	x	x
Citral	x	x	x
Citrus Aurantium Bergamia (Bergamot) Fruit Oil	x	x	x
Commiphora Myrrha Resin	x	x	x
Coriandrum Sativum (Coriander) Fruit Oil	x	x	x
Coumarin		x	x
Cuminum Cyminum (Cumin) Seed Oil		x	x
Cyclamen Aldehyde	x	x	
Decanal	x	x	x
Dimethylhydroquinone	x	x	x
Ethyl 3-methyl-3-phenyloxirane-2-carboxylate	x	x	x
Ethyl Benzoate		x	x
Ethyl hepanoate	x	x	x
Ethyl Vanillin		x	x
Eugenol		x	x
Gamma-Nonalactone	x	x	x
Gamma-Undecalactone	x	x	x

Fragrance Chemical	Irritant	Skin Irritant	Eye Irritant
Geraniol	x	x	x
Geranyl Acetate	x	x	x
Heliotropine	x	x	x
Hexamethylindanopyran	x	x	
Hexyl caproate	x	x	x
Hydroxycitronellal		x	x
Isoamyl Acetate		x	x
Juniperus Communis Fruit Oil		x	
Lavandula Angustifolia (Lavender) Oil		x	x
Linalool		x	x
Linalyl Acetate	x	x	x
Menthyl Acetate	x	x	x
Methyl 2-(methylamino)benzoate	x	x	x
Methyl Anthranilate	x	x	x
Methyl Benzoate		x	x
Methyl Cinnamate	x	x	x
Methyl Salicylate		x	x
Myristica Fragrans (Nutmeg) Kernel Oil	x	x	x
Myroxylon Balsamum (Balsam Tolu) Resin	x	x	
Myroxylon Pereirae (Balsam Peru) Oil	x	x	
Nonan-1-ol	x	x	x
Oils, styrax	x	x	x
p-Cresol		x	x
p-Cymene		x	x
Pelargonium Graveolens Flower Oil		x	x
Pentadecalactone		x	
Petitgrain oil, Paraguay	x	x	x
Phenethyl Acetate			x
Phenethyl Alcohol		x	x
Phenethyl Benzoate	x	x	x
Phenoxyethanol		x	x
phenylacetaldehyde		x	x
p-Methyl Acetophenone		x	x
Pogostemon Cablin Oil	x	x	x
Propanedioic acid, diethyl ester	x		x
Santalum Album (Sandalwood) Oil	x	x	x
Tanacetum vulgare, ext.		x	
Tartaric Acid		x	x
Terpineol	x	x	x

Fragrance Chemical	Irritant	Skin Irritant	Eye Irritant
Undecylenal		x	x
Vanillin			x
Vetiveria Zizanoides Root Oil		x	x

Figure 3 **Fragrance Chemicals Classified as an Irritant**

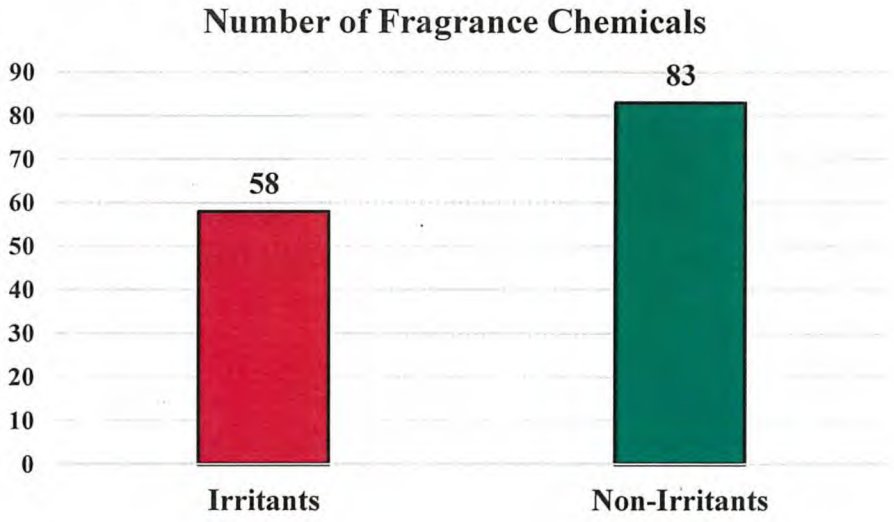


Figure 4 **Fragrance Chemicals Classified as a Skin Irritant**

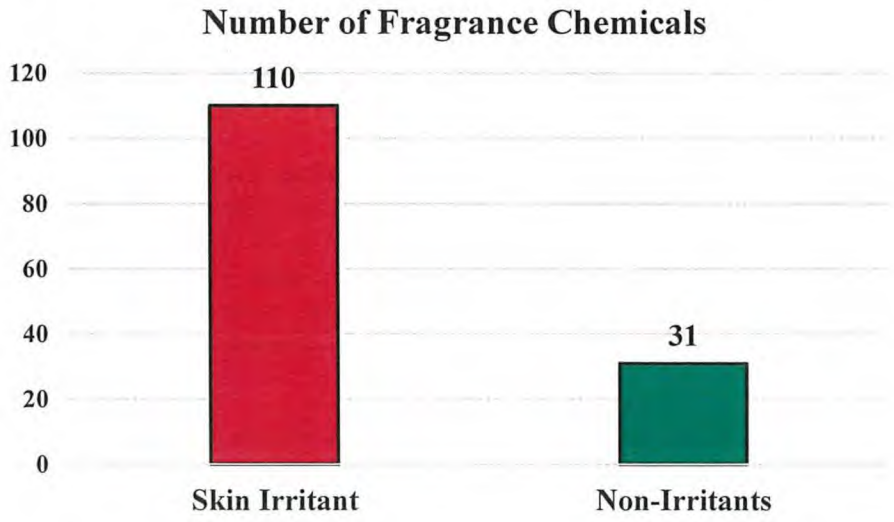
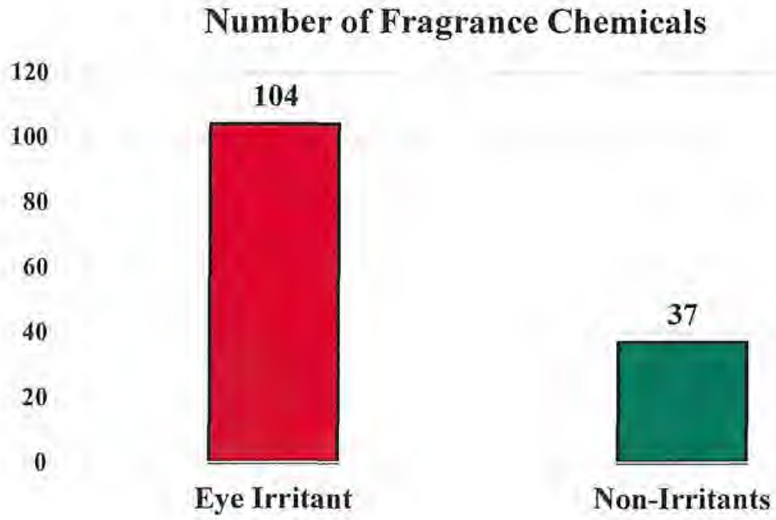


Figure 5 Fragrance Chemicals Classified as an Eye Irritant



4.5 Fragrance Chemicals Classified As Sensitizers

Sensitization is an adaptive response in the immune system and or exposure to allergen that results in the development of hypersensitivity. In this sense, sensitization is the term more often in usage for induction of allergic responses or hypersensitivity reaction. It is known that the induction of dermal sensitization is a threshold based phenomenon (Kimber et al., 2008; Robinson et al., 2000).

OSHA defines a sensitizer as "a chemical that causes a substantial proportion of exposed people or animals to develop an allergic reaction in normal tissue after repeated exposure to the chemical." The condition of being sensitized to a chemical is called chemical hypersensitivity.

Because sensitization is an immune response, some people may be easily sensitized while others may never be affected. Once a person is sensitized to a particular chemical, even minute amounts can cause symptoms. Sensitization is usually a life-long effect.

Traditionally, sensitization has been determined using animal testing. On April 10, 2018, the US EPA released a draft Science Policy to reduce the use of animals in testing chemicals to evaluate whether they cause an allergic reaction, inflammation or sensitization of the skin. The draft policy was open for public comment until June 9, 2018. The document is titled Draft Interim Science Policy: Use of Alternative Approaches for Skin Sensitization as a Replacement for Laboratory Animal Testing and describes the science behind the non-animal alternatives that can now be used (in vitro, in silico, in chemico) to identify skin sensitization.

The fragrance chemicals were reviewed to identify those that are classified as sensitizers according to the Globally Harmonized System of Classification and Labelling of Chemicals in accordance with 29 CFR 1910 (OSHA HCS). Fragrance Chemicals with R38, R 42/43, H317 or equivalent designations were classified as sensitizers. In addition, Fragrance Chemicals designated by IFRA as sensitizers were classified accordingly.

Of the 141 fragrance chemicals in the product, 39 fragrance chemicals are classified as sensitizers.

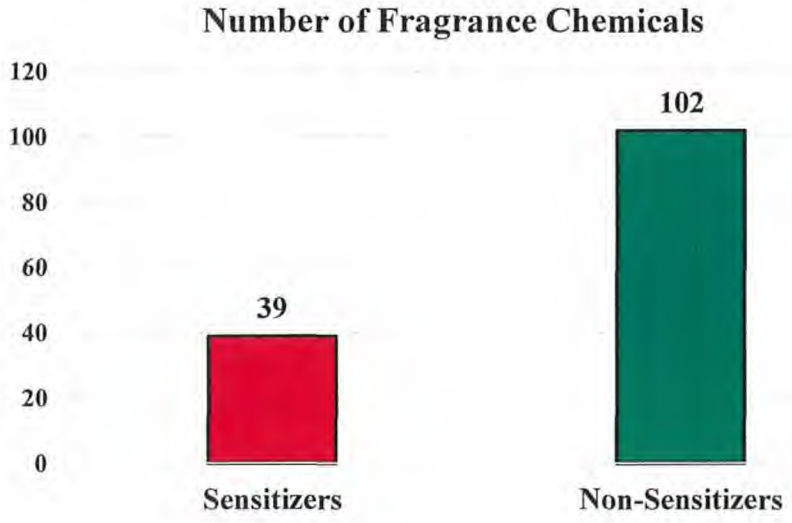
A summary of the findings is provided in Table 9 and a comparison of the number of fragrance chemicals designated as irritants, skin irritants and eye irritants are provided in Figure 6.

Table 9 Fragrance Chemicals Added to Johnson & Johnson Baby Powder Product with Sensitization Warnings

Fragrance Chemical	Sensitization
(d)-Limonene	x
1,2-Dimethoxy-4-prop-l-en-1-ylbenzene	x
1,7,7-Trimethylbicyclo[2,2,1]heptan-2-ol	x
1-acetonaphthone	x
2-Phenylethyl formate	x
3,7-Dimethyloct-6-en-l-ol	x
4-(2,6,6-Trimethylcyclohex-2-en-1-yl)but-3-en-2-one	x
Amyl Cinnamal	x
Benzyl Alcohol	x
Benzyl Benzoate	x
Benzyl Salicylate	x
Boswellia Carterii Oil	x
Carum Carvi (Caraway) Fruit Oil	x
Cinnamal	x
Cinnamyl Alcohol	x
Citral	x
Citrus Aurantium Bergamia (Bergamot) Fruit Oil	x
Coriandrum Sativum (Coriander) Fruit Oil	x
Coumarin	x
Eugenol	x
Geraniol	x
Hydroxycitronellal	x
Juniperus Communis Fruit Oil	x
Lavandula Angustifolia (Lavender) Oil	x
Linalool	x
Methyl 2-(methylamino)benzoate	x
Methyl Benzoate	x
Myristica Fragrans (Nutmeg) Kernel Oil	x
Myroxylon Balsamum (Balsam Tolu) Resin	x
Myroxylon Pereirae (Balsam Peru) Oil	x
Oils, styrax	x
Pelargonium Graveolens Flower Oil	x

Fragrance Chemical	Sensitization
Petitgrain Oil, Paraguay	x
phenylacetaldehyde	x
Santalum Album (Sandalwood) Oil	x
Tanacetum vulgare, ext.	x
Tartaric Acid	x
Undecylenal	x
Vetiveria Zizanoides Root Oil	x

Figure 6 Number of Fragrance Chemicals Classified as a Sensitization Hazard



4.6 Fragrance Chemicals Classified As Allergens and or Cause Contact Dermatitis

An allergen is a type of antigen that produces an abnormally vigorous immune response in which the immune system fights off a perceived threat that would otherwise be harmless to the body.

The fragrance chemicals were reviewed to identify those that are classified as allergens according to the Globally Harmonized System of Classification and Labelling of Chemicals in accordance with 29 CFR 1910 (OSHA HCS). Fragrance Chemicals with H317, H334 or equivalent designations were classified as allergens. Fragrance chemicals with literature reports of contact dermatitis were also classified accordingly.

Of the 141 fragrance chemicals in the product, 35 fragrance chemicals are classified as allergens and or cause contact dermatitis.

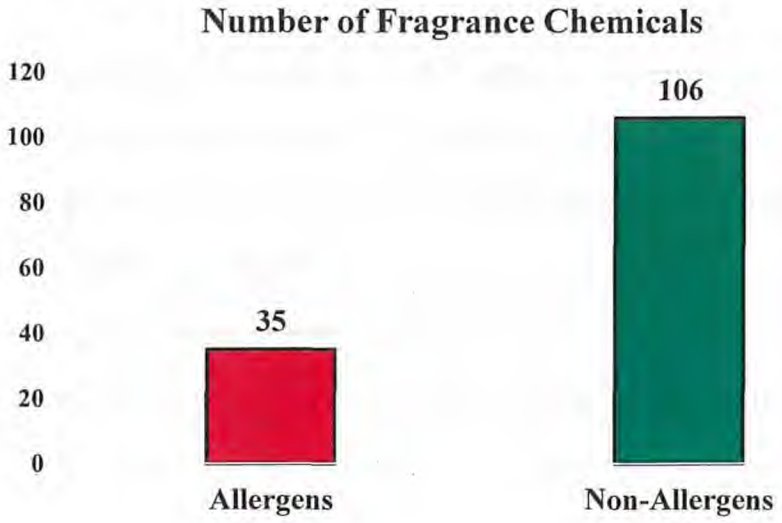
A summary of the findings is provided in Table 10 and a comparison of the number of fragrance chemicals designated as irritants, skin irritants and eye irritants are provided in Figure 7.

Table 10 Fragrance Chemicals Added to Johnson & Johnson Baby Powder Product Classified as Allergens and or Can Cause Contact Dermatitis

Fragrance Chemical	Allergen / Contact Dermatitis
(d)-Limonene	x
1-(2,6,6-Trimethylcyclohex-2-en-1-yl)pent-1-en3-one	x
1,2-Dimethoxy-4-prop-l-en-1-ylbenzene	x
1-acetonaphthone	x
1-Benzazole	x
1-Cedr-8-en-9-ylethanone	x
2-Isopropyl-5-methylcyclohexanol	x
2-Phenylethyl formate	x
3,7-Dimethyloct-6-en-l-ol	x
3,7-Dimethylocta-2,6-dien-1-yl acetate	x
5-Isopropenyl-2-methylcyclohex-2-en-1-one	x
Alpha-Isomethyl Ionone	x
Amyl Cinnamal	x
Benzaldehyde	x
Benzyl Salicylate	x
Cinnamal	x
Cinnamyl Alcohol	x
Citral	x
Citrus Aurantium Bergamia (Bergamot) Fruit Oil	x
Cyclamen Aldehyde	x
Eugenol	x
Geraniol	x
Geranyl Acetate	x
Heliotropine	x
Hydroxycitronellal	x
Linalool	x
Methyl Benzoate	x
Methyl Cinnamate	x
Oils, styrax	x
Pentadecalactone	x
Petitgrain oil, Paraguay	x
phenylacetaldehyde	x

Fragrance Chemical	Allergen / Contact Dermatitis
Tartaric Acid	x
Undecylenal	x
Vetiveria Zizanoides Root Oil	x

Figure 7 **Fragrance Chemicals Classified as Allergens and or Cause Contact Dermatitis**



4.7 Fragrance Chemicals with IFRA Critical Effects

The fragrance industry has maintained a system of safety assurance since 1973. IFRA sets standards that are intended to ensure the safe use of fragrance ingredients for the consumer and the environment. IFRA Standards are based on a scientific assessment of potential hazards (extensive set of toxicological data) and comprehensive information on the use of and exposure to fragrance materials by RIFM and subsequent evaluation by the RIFM expert panel.

RIFM is the scientific institute for the fragrance industry and is responsible for generating, evaluating and distributing scientific data on the safety of fragrance materials in consumer products. The scientific program at RIFM is guided by the RIFM expert panel. RIFM's scientific information is published in peer reviewed journals. The Expert Panel's conclusions include definition of critical effects and a safety evaluation based upon reported use. The process of RIFM risk assessment has been described (David R. Bickers et al., 2003)

The fragrance chemicals were reviewed to identify those that are designated with an IFRA Critical Effect.

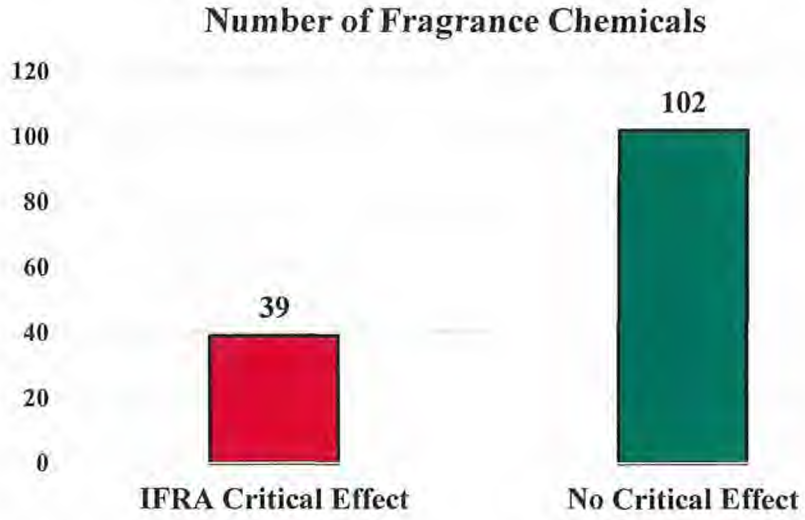
Of the 141 fragrance chemicals in the product, 39 fragrance chemicals have an IFRA Critical Effect. A summary of the findings is provided in Table 11 and a comparison of the number of fragrance chemicals designated with an IFRA Critical Effect is provided in Figure 8.

Table 11 Fragrance Chemicals Added to Johnson & Johnson Baby Powder Product with IFRA Critical Effects

Fragrance Chemical	IFRA Critical Effect
(d)-Limonene	Sensitization
1-(2,6,6-Trimethylcyclohex-2-en-1-yl)pent-1-en3-one	Dermal sensitization
2-Acetonaphthone	Phototoxicity
3,7-Dimethyloct-6-en-l-ol	Sensitization
4-(2,5,6,6-Tetramethylcyclohex-2-en-1-yl)but-3-en-2-one	Sensitization
5-Isopropenyl-2-methylcyclohex-2-en-1-one	Sensitization
Alpha-Isomethyl lonone	Dermal sensitization
Amyl Cinnamal	Sensitization
Anisaldehyde	Sensitization
Benzaldehyde	Sensitization
Benzyl Alcohol	Sensitization
Benzyl Benzoate	Sensitization
Benzyl Salicylate	Sensitization
Cedrus Atlantica (Cedarwood) Bark Oil	Sensitization
Cinnamal	Sensitization
Cinnamyl Alcohol	Sensitization
Citral	Sensitization
Citrus Aurantium Bergamia (Bergamot) Fruit Oil	Phototoxicity
Citrus Aurantium Dulcis (Orange) Peel Oil	Phototoxicity
Citrus Medica Limonum (Lemon) Peel Oil	Phototoxicity
Coriandrum Sativum (Coriander) Fruit Oil	Sensitization
Coumarin	Sensitization
Cuminum Cyminum (Cumin) Seed Oil	Phototoxicity
Cyclamen Aldehyde	Dermal sensitization
Eugenol	Sensitization
Evernia Prunastri (Oakmoss) Extract	Sensitization
Geraniol	Sensitization
Hydroxycitronellal	Sensitization
Lavandula Angustifolia (Lavender) Oil	Sensitization
Lemon oil terpenes	Phototoxicity
Linalool	Sensitization
Methyl 2-(methylamino)benzoate	Phototoxicity and potential for nitrosamine formation

Fragrance Chemical	IFRA Critical Effect
Myristica Fragrans (Nutmeg) Kernel Oil	Sensitization
Myroxylon Pereirae (Balsam Peru) Oil	Sensitization
Oils, styrax	Sensitization
Opoponax	Sensitization
Pentadecalactone	Sensitization
Petitgrain oil, Paraguay	Sensitization
phenylacetaldehyde	Sensitization

Figure 8 Fragrance Chemicals with IFRA Critical Effects



4.8 Fragrance Chemicals with IFRA Category 5 Restrictions

IFRA & RIFM developed the Quantitative Risk Assessment (QRA) to determine safe use levels of fragrance ingredients in a variety of consumer product types (Api & Vey, 2008b; IFRA & RIFM, 2015; McNamee et al., 2008; Politano & Api, 2008). The QRA specifically addresses the elements of exposure-based risk assessment that are unique to the induction of dermal sensitization, while being consistent with the principles of general toxicology risk assessment. The QRA is an improvement over the risk management strategies formerly used by IFRA, in which each specific fragrance ingredient identified as an allergen was limited to the same concentration across all skin contact product types (Api et al., 2008).

IFRA has "capped" the usage levels on certain fragrances due to dermal sensitization and allergic response concerns (Cowan-Ellsberry, McNamee, & Leazer, 2008; Kimber et al., 2008). The restrictions are retrospective, based on old methodology, and prospective, based upon the QRA system (Api & Vey, 2008a). Standards that impose a quantitative limit on the use of fragrance materials are expressed as a maximum concentration of fragrance material in the consumer product. This implies knowledge of the

concentration of the restricted fragrance material in the compound and the concentration of the compound in the final consumer product. Fragrance suppliers are therefore required to inform manufacturers of consumer products, who use or intend to use a fragrance compound, that due to the presence of a restricted ingredient, the compound should only be used up to a specified maximum concentration or in well-defined applications, thereby being in compliance with IFRA Standards. Unless otherwise specified, concentrations are expressed in weight-weight percent.

From the 40th Amendment on, the Standards limiting ingredients due to sensitization are based on the Quantitative Risk Assessment for dermal sensitizers (QRA). The QRA methodology for fragrance ingredients is a refined risk assessment approach for dermal sensitizers, which currently identifies individual limitations for 11 specific product categories (based on similar Safety Assessment Factors and exposure).

"Baby Powder and Talcs" have been assigned to Category 5. Category 5 also includes Women's Facial Creams/Facial Make-up, Hand Cream, Facial Masks, Hair Permanent and other hair chemical treatments (e.g. relaxers) but not hair dyes, Wipes or Refreshing Tissues for Face, Neck, Hands, Body, Hand Sanitizers and Dry Shampoo or Waterless Shampoo.

The fragrance chemicals were reviewed to identify those that are designated with a Category 5 Restriction.

Of the 141 fragrance chemicals in the product, 23 fragrance chemicals have a Category 5 Restriction. A summary of the findings is provided in Table 12 and a comparison of the number of fragrance chemicals designated with a Category 5 Restriction is provided in Figure 9.

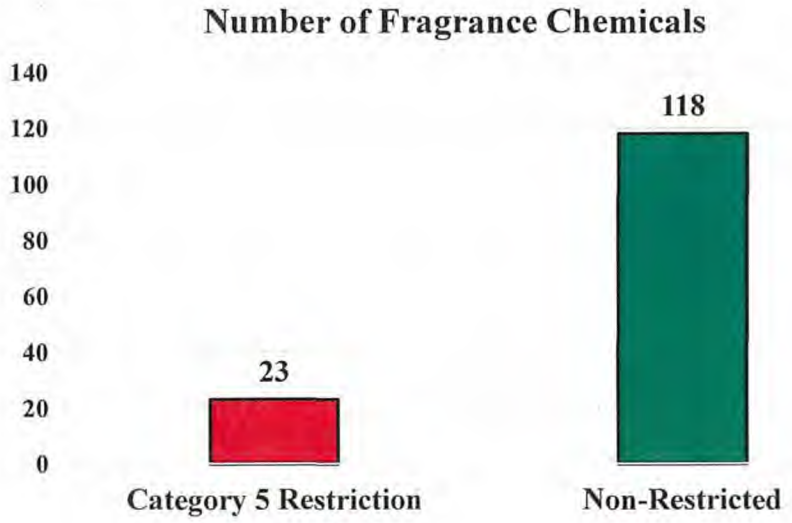
An example of how the QRA examines fragrance ingredients was published on Citral, one of the fragrance ingredients in the Baby Powder product (Jon Lalko & Api, 2008).

Table 12 Fragrance Chemicals Added to Johnson & Johnson Baby Powder Product with IFRA Category 5 Restriction

Fragrance Chemical	Category 5 Restriction
1-(2,6,6-Trimethylcyclohex-2-en-1-yl)pent-1-en3-one	16.67
3,7-Dimethyloct-6-en-1-ol	7.00%
5-Isopropenyl-2-methylcyclohex-2-en-1-one	0.60%
Alpha-Isomethyl Ionone	16.67%
Amyl Cinnamal	5.60%
Anisaldehyde	0.84%
Benzaldehyde	0.14%
Benzyl Alcohol	1.40%
Benzyl Benzoate	14.00%
Benzyl Salicylate	4.20%
Cinnamal	0.05%
Cinnamyl Alcohol	0.40%
Citral	0.30%

Fragrance Chemical	Category 5 Restriction
Coumarin	0.80%
Cyclamen Aldehyde	1.40%
Eugenol	0.50%
Evernia Prunastri (Oakmoss) Extract	0.10%
Geraniol	2.80%
Hydroxycitronellal	1%
Oils, styrax	0.36%
Opoponax	0.24%
Pentadecalactone	1.31%
phenylacetaldehyde	0.10%

Figure 9 **Fragrance Chemicals with a Category 5 Restriction**



4.9 Fragrance Chemicals with Exposure Limits

Prior to the QRA, IFRA & RIFM established exposure limits. Exposure limits for these chemicals were established to reduce the risk of dermal sensitization and as such, are not related to considerations of safe levels for ingestion. These limits remain as part of an IFRA standard if a specific fragrance has not been through the QRA process.

The fragrance chemicals were reviewed to identify those that are designated with Exposure Limits.

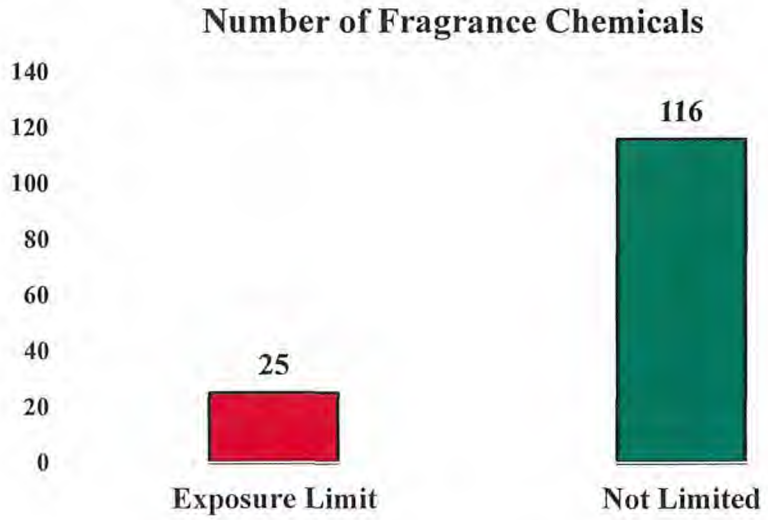
Of the 141 fragrance chemicals in the product, 25 fragrance chemicals have an Exposure Limit. A summary of the findings is provided in Table 13 and a comparison of the number of fragrance chemicals designated with an Exposure Limit is provided in Figure 10.

Table 13 Fragrance Chemicals Added to Johnson & Johnson Baby Powder Product with Exposure Limits

Fragrance Chemical	Dermal Exposure Limit
1,7,7-Trimethylbicyclo[2,2,1]heptan-2-ol	0.0140 mg/kg/day (IFRA, 2006)
2-Acetonaphthone	0.2% leave on the skin contact
2-Isopropenyl-5-methylcyclohexanol	0.0007 mg/kg/day (IFRA, 2004)
2-Isopropyl-5-methylcyclohexanol	0.0074 mg/kg/day (IFRA, 2004)
3,7-Dimethylocta-2,6-dien-1-yl benzoate	0.5% leave on skin contact
3-Methyl-1H-indole	0.10 % in the fragrance concentrate.
4-(2,5,6,6-Tetramethylcyclohex-2-en-1-yl)but-3-en-2-one	0.29% maximum skin levels for fine fragrances, 0.22% for cosmetics; 0.0055 mg/kg/day (IFRA, 2001)
4-(2,6,6-Trimethylcyclohex-2-en-1-yl)but-3-en-2-one	Use level in formulae for use in cosmetics: 2.0100%; Dermal Systemic Exposure in Cosmetic Products: 0.05 mg/kg/day (IFRA, 2002)
Alpha-Isomethyl Ionone	Use level in formulae for use in cosmetics: 13.0%; Dermal Systemic Exposure in Cosmetic Products: 0.33 mg/kg/day (IFRA, 2001)
Benzoic acid, 2-hydroxy-, 2-methylpropyl ester	Dermal Systemic Exposure in Cosmetic Products: 0.0043 mg/kg/day (IFRA, 2002); maximum skin levels for fine fragrances: 0.81%
Benzoic acid, 2-hydroxy-, ethyl ester	Dermal Systemic Exposure in Cosmetic Products: 0.0002 mg/kg/day (IFRA, 2002); maximum skin levels for fine fragrances: 0.14%
Benzyl Salicylate	Dermal Systemic Exposure in Cosmetic Products: 0.40 mg/kg/day (IFRA, 2002)
Citrus Aurantifolia (Lime) Oil	Limits in the finished product for - "leave on the skin contact": 0.7000 % Restriction. Recommendation for lime oil usage levels up to: 15.0000 % in the fragrance concentrate.
Citrus Aurantium Bergamia (Bergamot) Fruit Oil	Limits in the finished product for - ""leave on the skin contact"": 0.4000 % Restriction"
Citrus Aurantium Dulcis (Orange) Peel Oil	Limits in the finished product for - "leave on the skin contact": 2.0000 % Restriction.
Citrus Medica Limonum (Lemon) Peel Oil	Limits in the finished product for - "leave on the skin contact": 2.0000 % Restriction.
Cuminum Cyminum (Cumin) Seed Oil	Limits in the finished product for - "leave on the skin contact": 0.4000 % Restriction. Recommendation for cumin seed oil usage levels up to: 5.0000 % in the fragrance concentrate.

Fragrance Chemical	Dermal Exposure Limit
Ethyl Benzoate	Limits in the finished product for - "leave on the skin contact": 0.50% Recommendation.
Linalool	Maximum skin levels for fine fragrances: 4.3000 %; Dermal Systemic Exposure in Cosmetic Products: 6.3236 mg/kg/day (IFRA, 2002)
Methyl 2-(methylamino)benzoate	Limits in the finished product for - "leave on the skin contact": 0.1000 % Restriction;
Methyl Benzoate	Limits in the finished product for - "leave on the skin contact": 0.50 % Recommendation.
Methyl Cinnamate	Maximum skin levels for fine fragrances: 0.3100 %; use level in formulae for use in cosmetics: 0.21 %; Dermal Systemic Exposure in Cosmetic Products: 0.0054 mg/kg/day (IFRA, 2001)
Methyl Salicylate	Use level in formulae for use in cosmetics: 0.1300 %; Dermal Systemic Exposure in Cosmetic Products: 0.0034 mg/kg/day (IFRA, 2002)
p-Cresol	Recommendation for para-cresol usage levels up to: 0.0500 % in the fragrance concentrate.
Terpineol	Dermal Systemic Exposure in Cosmetic Products: 0.0744 mg/kg/day (IFRA, 2003)

Figure 10 Fragrance Chemicals with an Exposure Limit



4.10 Fragrance Chemicals Listed on the FDA Inactive Ingredient Database (IID)

The US Food and Drug Administration maintains the Inactive Ingredient Database (IID). The Inactive Ingredient Database provides information on inactive ingredients present in FDA-approved drug products. In general, inactive ingredients on this list have been subject to extensive toxicology studies for a given route of administration.

When a new drug product is submitted to the FDA, the agency reviews the inactive ingredients used in that drug product. FDA considers the amount of each inactive ingredient, the route of administration (i.e. oral, injection, transdermal, otic, vaginal, ophthalmic), and whether the inactive ingredients have demonstrated safety for each specific route. If an inactive ingredient has not previously been approved for the route of administration, FDA requests that the sponsor demonstrate safety.

The fragrance chemicals were reviewed to identify those listed on the FDA IID, including those listed for topical administration (applied to the skin) and vaginal administration.

Of the 141 fragrance chemicals in the product, 26 fragrance chemicals are listed on the FDA IID, 9 are present in an approved drug products for topical administration and 1 is present in an approved drug product for vaginal administration.

FDA and EFSA consider oral administration for flavors. IFRA and CIR consider topical administration (i.e. application to the skin) for fragrances and cosmetic ingredients. In this matter, the talcum products were applied to the perineal area. An unintended consequence of perineal application of the talcum products would be transport into the vaginal cavity and exposure to the vagina, endometrium, fallopian tubes and ovaries. The safety margins of 140 of the fragrance chemicals were determined for foods (oral administration) or cosmetics (topical application to the skin), except for the 1 fragrance chemical on the FDA IID in an approved drug product administered to the vagina.

A summary of the findings is provided in Table 14 and a comparison of the number of fragrance chemicals on the FDA IID in Figure 11, on the IID for topical administration in Figure 12 and on the IID for vaginal administration in Figure 13.

Table 14 Fragrance Chemicals Added to Johnson & Johnson Baby Powder Product Listed on the FDA IID

Fragrance Chemical	IID Listed	IID Listed for Topical Admin	IID Listed for Vaginal Admin
(d)-Limonene	x	x	
2-Isopropyl-5-methylcyclohexanol	x	x	
2-Propanol, 1,1'-oxybis-	x	x	
5-Isopropenyl-2-methylcyclohex-2-en-1-one	x		
Acetic acid, phenylmethyl ester	x		
Benzaldehyde	x		
Benzyl Alcohol	x	x	x
Benzyl Benzoate	x		
Butanoic acid, ethyl ester	x		
Citrus Aurantium Dulcis (Orange) Peel Oil	x		

Fragrance Chemical	IID Listed	IID Listed for Topical Admin	IID Listed for Vaginal Admin
Citrus Medica Limonum (Lemon) Peel Oil	x		
Citrus Nobilis (Mandarin Orange) Peel Oil	x		
Coriandrum Sativum (Coriander) Fruit Oil	x		
Ethyl Vanillin	x		
Eugenol	x		
Isoamyl Acetate	x		
Methyl Salicylate	x		
Myristica Fragrans (Nutmeg) Kernel Oil	x		
Myroxylon Balsamum (Balsam Tolu) Resin	x		
Myroxylon Pereirae (Balsam Peru) Oil	x		
Pentadecalactone	x	x	
Phenethyl Alcohol	x	x	
Phenoxyethanol	x	x	
Tartaric Acid	x	x	
Terpineol	x	x	
Vanillin	x		

Figure 11 Fragrance Chemicals Listed on the FDA IID

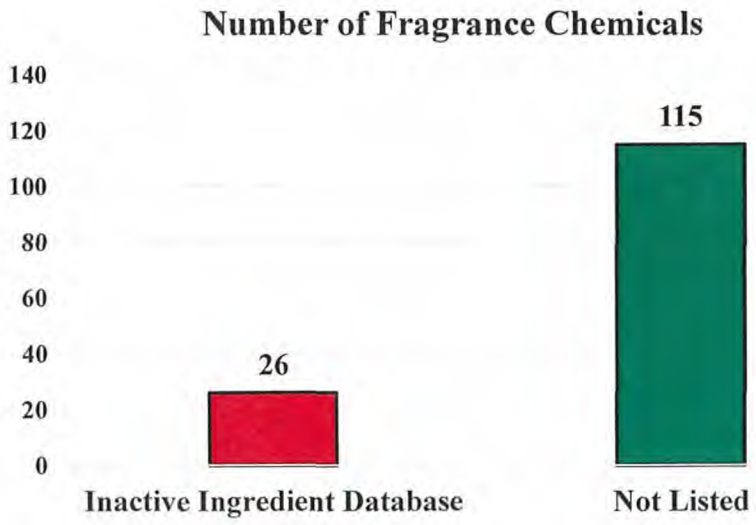


Figure 12 **Fragrance Chemicals Listed on the FDA IID for Topical Administration**

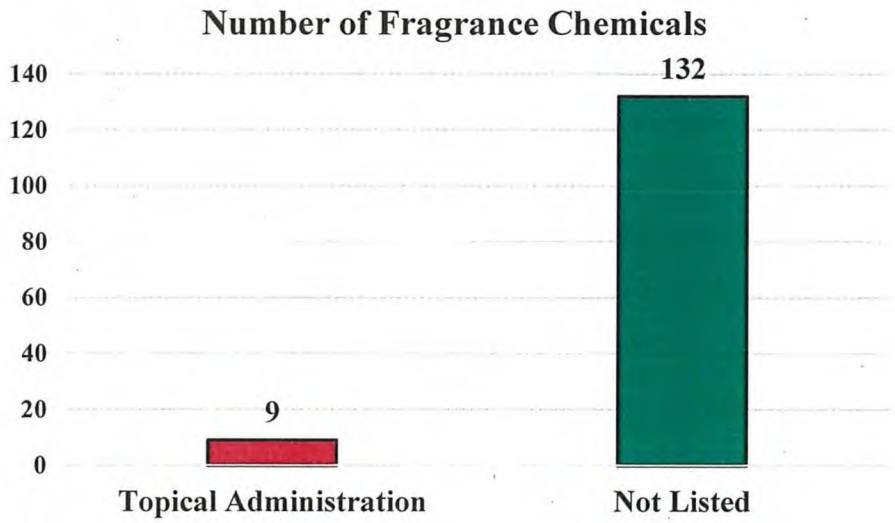
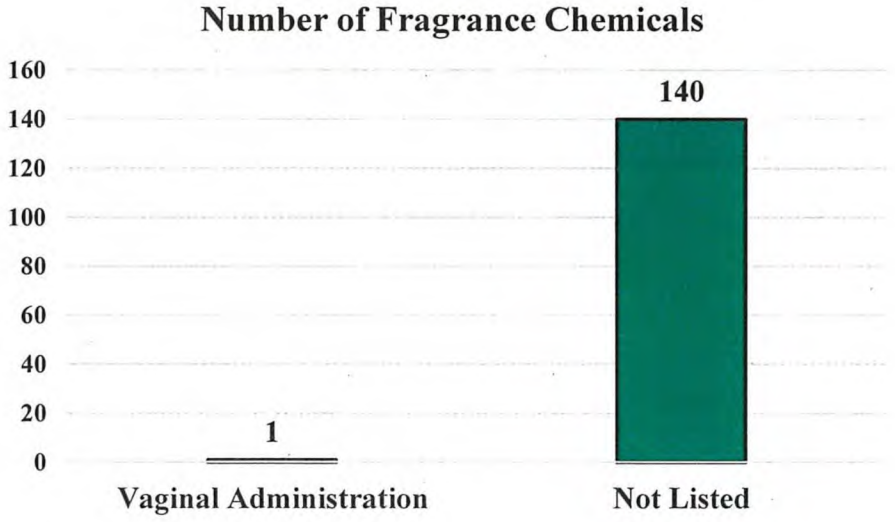


Figure 13 **Fragrance Chemicals Listed on the FDA IID for Vaginal Administration**



5 FRAGRANCE CHEMICALS IN JOHNSON & JOHNSON SHOWER TO SHOWER PRODUCT

The Johnson & Johnson Shower to Shower product contains 53 fragrance chemicals. Some of these fragrances are themselves a mixture of chemicals.

5.1 Unidentified Fragrance Chemicals

One fragrance chemicals could not be identified: Indisan (Sandela) reaction product.

5.2 Fragrance Chemical Regulatory Review

As described in Section 4.2, a regulatory review of the fragrance chemicals was performed. Eighteen (18) fragrance chemicals in the Johnson & Johnson Shower to Shower product were identified that are either (1) not listed in Title 21 of the Code of Federal Regulations, (2) not approved for fragrance of flavor use, (3) not permitted for cosmetic use, (4) requires warnings, (5) are not permitted for use on the body, (6) absence of an IFRA Standard and or (7) absence of a CIR listing, or a CIR listing as unsafe or insufficient data to support safety.

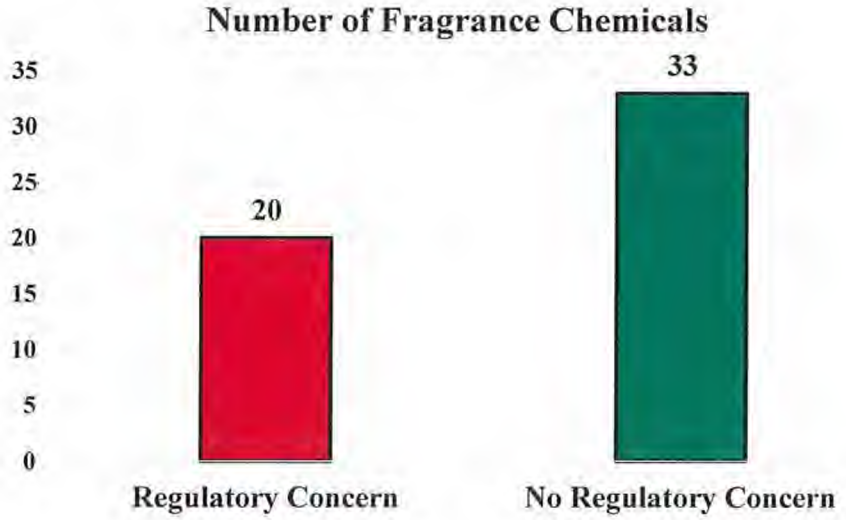
A summary of the fragrance chemicals with regulatory concerns is provided in Table 15. A comparison of the number of fragrance chemicals with regulatory concerns to the total number of fragrance chemicals is provided in Figure 14.

Table 15 Fragrance Chemicals Added to Johnson & Johnson Shower to Shower Product with Regulatory Concerns

Fragrance Chemical	Regulatory Concern
1-Cedr-8-en-9-ylethanone	Not listed in CFR Title 21 No IFRA Standard Not listed by CIR
2-Nonanone, 3-(hydroxymethyl)-	Not listed in CFR Title 21 No IFRA Standard Not listed by CIR
2-Octanol, 2,6-dimethyl	Not listed in CFR Title 21 No IFRA Standard Not listed by CIR
2-Propanol, 1,1'-oxybis-	Not listed in CFR Title 21 No IFRA Standard
2-t-Butylcyclohexyl Acetate	Not listed in CFR Title 21 No IFRA Standard Not listed by CIR
3,7-Dimethylnona-2,6-dienenitrile	Not listed in CFR Title 21 No IFRA Standard Not listed by CIR
3-Cyclohexene-1-carboxaldehyde, 3-(4-hydroxy-4-methylpentyl)-	Not listed in CFR Title 21 Not Listed by CIR

Fragrance Chemical	Regulatory Concern
4,7-Methano-IH-indenol, 3a,4,5,6,7,7a-hexahydro-, propanoate	Not listed in CFR Title 21 No IFRA Standard Not listed by CIR
Acetic acid, anhydride, reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene	Not listed in CFR Title 21 Not listed by CIR
Acetic acid, p-tert-butylcyclohexyl ester	Not listed in CFR Title 21 No IFRA Standard Not listed by CIR
Aloe Barbadensis Leaf Extract	Not a fragrance No IFRA Standard
Benzophenone	No longer listed in the CFR for food use. No IFRA Standard
Citronellyl Nitrile	Not listed in CFR Title 21 No FDA UNII No EFSA No FEMA or IFRA standard Not Listed by CIR
Coumarin	Prohibited in foods (banned in 1954) Not listed by CIR
Diethyl Phthalate	Not a fragrance, FDA: Indirect food contact No IFRA Standard
Hexamethylindanopyran	Not listed in CFR Title 21 Not listed by CIR
Indisan (Sandela) reaction product	Could not locate any information
Isopropyl Palmitate	Not a fragrance No IFRA Standard
Musk Ketone	Not listed in CFR Title 21
Propylene Glycol	Not a fragrance No IFRA Standard
TBHQ (t-butyl hydroquinone)	Not a fragrance No IFRA Standard
Tromethamine	Not a fragrance No IFRA Standard

Figure 14 Fragrance Chemicals with Regulatory Concerns



5.3 Fragrance Chemical Safety and Toxicology Review

As described in Section 4.3, the fragrance chemicals in Shower to Shower were reviewed for safety and toxicology. Thirteen (13) fragrance chemicals were found to be listed on the RTECS list (Registry of Toxic Effects of Chemical Substances) or had safety in use concerns.

Three fragrance chemicals added to J&J's Shower to Shower talcum product are included in the IARC monographs as possible carcinogens. Benzophenone has been classified by IARC as a Group 2B possible human carcinogen (International Agency for Research on Cancer (IARC), 2013b). Coumarin and eugenol are "not classifiable" as to their carcinogenicity (Group 3). In addition, Musk ketone is suspected of being a carcinogen, and has been classified as a Category 3 carcinogen by the Scientific Committee on Health and Environmental Risks (SCHER) in Europe. The remainder of the fragrance chemicals in the Shower to Shower product have not been evaluated by IARC as to their carcinogenicity.

Diethyl Phthalate, a non-fragrance present as a component in the fragrance mixture, is a phthalate ester which are reported to be endocrine disruptors, cause reproductive and developmental toxicities, and potentially genotoxic (Al-Saleh, Al-Rajudi, Al-Qudaihi, & Manogaran, 2017).

Benzophenone was recently removed from use in foods by FDA (U.S. Food and Drug Administration, 2018) due to histiocytic sarcoma observed in ovaries and uterus, higher incidences of kidney tumors and leukemia in animal studies (National Toxicology Program (NTP), 2006), and in vivo estrogenic activity (International Agency for Research on Cancer (IARC), 2013a).

Similarly, equivocal evidence of carcinogenic activity of Diethyl Phthalate in male and female B6C3F1 mice based on increased incidences of hepatocellular neoplasms, primarily adenomas, has been reported (National Toxicology Program (NTP), 1995).

Several chemicals in the fragrance mixture used in the J&J talcum products were identified with in vitro and in vivo studies published in peer reviewed journals demonstrating carcinogenicity, developmental or

reproductive toxicity, genotoxicity, and/or mutagenicity. While these studies are not definitive that the same effects would be observed in humans, they are indicators of biological activity.

A summary of the findings is provided in Table 16 and a comparison of the number of fragrance chemicals with safety and toxicology concerns to the total number of fragrance chemicals in the product is provided in Figure 15.

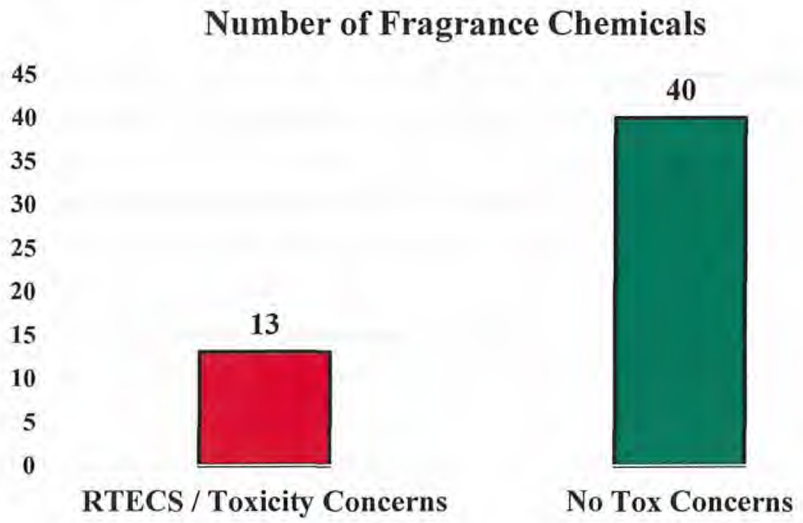
Table 16 Fragrance Chemicals Added to Johnson & Johnson Shower to Shower Product on the RTECS List and or Toxicity Concerns

Fragrance Chemical	RTECS	Toxicity Concern
1-Methoxy-4-methylbenzene		H361: Suspected of damaging fertility or the unborn child H361 Reproductive toxicity (Category 2)
2-Propanol, 1,1'-oxybis-	x	
Benzophenone	x	H351 Carcinogenicity (Category 2), Suspected of causing cancer H373: Causes damage to organs through prolonged or repeated exposure [Warning Specific target organ toxicity, repeated exposure] "Male rats receiving benzophenone had more severe kidney nephropathy than control animals and higher incidences of kidney tumors and leukemia. Female rats receiving benzophenone also had slightly higher rates of leukemia. Male and female mice had slightly increased rates of liver tumors and also increased severities of kidney nephropathy, metaplasia of the epithelium of the nose, and hyperplasia of the spleen. Some female mice also developed rare histiocytic sarcomas." (National Toxicology Program (NTP), 2006) "We conclude that benzophenone caused kidney cancer in male rats, liver tumors in male mice, and histiocytic sarcomas in female mice. Benzophenone may also have been associated with development of leukemia in male and female rats and with liver tumors in female mice." (National Toxicology Program (NTP), 2006) "Histiocytic Sarcoma: In females, there was a positive trend in the incidences of histiocytic sarcoma (all organs); the incidence in 625 ppm females was significantly greater than that in the controls (Tables 17 and D3). Only two histiocytic sarcomas have been observed in historical feed study controls, and the incidence in the 625 ppm group exceeded the historical control range for all routes (Tables 17 and D4). In the current 2-year study, only females were affected, and the liver and

Fragrance Chemical	RTECS	Toxicity Concern
		lung were involved in all affected females. The histiocytic sarcomas were highly invasive in all three 1,250 ppm mice. Multiple organs throughout the body had neoplastic histiocytic lesions. **Ovary, uterus, spleen, adrenal gland, kidney, urinary bladder, and multiple lymph nodes were affected in all three animals.**" (National Toxicology Program (NTP), 2006) "The in vivo estrogenic activity of benzophenone was confirmed in the uterotrophic assay"(International Agency for Research on Cancer (IARC), 2013a) "Morphological examination showed that the treatment increased the luminal epithelial height and the thickness of the stromal layer of the uterus due to proliferation of uterine luminal epithelial cells, and increased the thickness and induced cornification of the vaginal epithelium." (International Agency for Research on Cancer (IARC), 2013a) "The estrogen-like effects of benzophenone in the female reproductive tract appear to be due to metabolism to 4-hydroxybenzophenone, which binds to ERα" (International Agency for Research on Cancer (IARC), 2013a) Benzophenone is possibly carcinogenic to humans (Group 2B) (International Agency for Research on Cancer (IARC), 2013b)
Benzyl Benzoate	x	
Benzyl Salicylate	x	BzS showed obvious in vitro hERα agonistic activities; BzS in particular exhibited a higher estrogenic activity compared to bisphenol A (BPA) (Zhang et al., 2012).
Coumarin	x	Recent evidence indicates coumarin causes liver tumors in rats and mice and Clara cell toxicity and lung tumors in mice (Wishart, 2018). Reproductive: Effects on embryo or fetus: Fetotoxicity (except death, e.g., stunted fetus) in rats (RTECS) Sister chromatid exchange (mutation) in Chinese Hamster Ovary cells (Galloway et al., 1987). IARC potential carcinogen (International Agency for Research on Cancer (IARC), 2000)

Fragrance Chemical	RTECS	Toxicity Concern
		Sister chromatid exchange (mutation) and chromosomal abberrations in Chinese Hamster Ovary cells (National Toxicology Program (NTP), 1993)
Diethyl Phthalate	x	Phthalate esters can cause reproductive and developmental toxicity. (RTECS) "In cultured Chinese hamster ovary cells, both diethylphthalate and dimethylphthalate induced sister chromatid exchanges in the presence of S9. (167 to 750 µg/mL)" (National Toxicology Program (NTP), 1995) "There was equivocal evidence of carcinogenic activity of. diethylphthalate in male and female B6C3F1 mice based on increased incidences of hepatocellular neoplasms, primarily adenomas" (National Toxicology Program (NTP), 1995)
Eugenol		IARC potential carcinogen (Group 3 "not classifiable") (International Agency for Research on Cancer (IARC), 1985) Sister Chromatid Exchange (11 – 123 µg/mL) and Chromosome Aberration in Chinese Hamster Ovary Cells (198 – 300 µg/mL) (Galloway et al., 1987).
Isopropyl Palmitate	x	
Methyl Benzoate	x	"Methyl benzoate was cytotoxic to HeLa cells at 683.30 mmol/L, A flavus at 2.5 mg/mL, A parasiticus at 5.0 mg/mL, and lung fibroblasts at 25 mmol/L." "Not only caused toxic effects to the cells but also promoted membrane penetration by other substances" (Becker et al., 2012).
Musk Ketone	x	"classify musk ketone as "category 3 carcinogen" based on read across." (Scientific Committee On Health And Environmental Risks (SCHER), 2006) "Musk Ketone was identified as a strong inducer of phase I enzymes in rodents and a co-genotoxicant in vitro in human derived cells in rather low doses, suggesting that exposure to Musk Ketone might increase the susceptibility to health hazards caused by carcinogens in humans." (Schmeiser, Gminski, & Mersch-Sundermann, 2001)
Phenethyl Alcohol	x	Mutation and Reproductive Effects (RTECS)
Propylene Glycol	x	

Figure 15 Fragrance Chemicals with Toxicity Concerns



5.4 Fragrance Chemicals Classified As Irritants

As described in Section 4.3, the fragrance chemicals in the Shower to Shower product were reviewed for classification as an irritant.

Of the 53 fragrance chemicals in the product, 25 fragrance chemicals are designated as irritants, 44 are designated as skin irritants and 40 are eye irritants.

A summary of the findings is provided in Table 17 and a comparison of the number of fragrance chemicals designated as irritants, skin irritants and eye irritants are provided in Figure 16, Figure 17 and Figure 18.

Table 17 Fragrance Chemicals Added to Johnson & Johnson Shower to Shower Product Listed as Irritants, Skin Irritants and Eye Irritants

Fragrance Chemical	Irritant	Skin Irritant	Eye Irritant
1-Benzazole		x	x
1-Cedr-8-en-9-ylethanone		x	x
1-Methoxy-4-methylbenzene		x	x
2,6-Dimethylheptan-2-ol	x	x	x
2-Acetonaphthone		x	x
2-Nonanone, 3-(hydroxymethyl)-		x	x
2-Octanol, 2,6-dimethyl	x	x	x
2-Propanol, 1,1'-oxybis-		x	x
3,7-Dimethyloct-6-en-l-ol	x	x	x
3,7-Dimethylocta-2,6-dien-1-ol	x	x	x

Fragrance Chemical	Irritant	Skin Irritant	Eye Irritant
3-Cyclohexene-l-carboxaldehyde, 3-(4-hydroxy-4-methylpentyl)-			
3-Methylbutyl salicylate	X	X	X
3-Octanol, 3,7-dimethyl-	X	X	X
4,7-Methano-IH-indenol, 3a,4,5,6,7,7a-hexahydro-, propanoate		X	
Acetic acid, anhydride, reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene	X	X	X
Acetic acid, p-tert-butylcyclohexyl ester	X	X	X
Aloe Barbadensis Leaf Extract			
Amyl Cinnamal	X	X	X
Amyris Balsamifera Bark Oil		X	X
Anthemis Nobilis Flower Oil	X	X	
Benzophenone	X	X	X
Benzyl Benzoate		X	X
Benzyl Salicylate		X	X
Cinnamyl Alcohol	X	X	X
Citronellyl Nitrile	X	X	X
Commiphora Myrrha Oil		X	X
Coumarin		X	X
Cyclamen Aldehyde	X	X	
Diethyl Phthalate		X	X
Dihydrocitronellol	X	X	X
Eugenol	X	X	X
Geraniol	X	X	X
Hexamethylindanopyran	X	X	
Hexane, 1-methoxy-	X	X	
Isoeugenol	X	X	X
Isopropyl Palmitate		X	X
Levisticum Officinale Oil	X	X	X
Methyl Benzoate		X	X
Myristica Fragrans (Nutmeg) Kernel Oil	X	X	X
Octan-2-one		X	X
Phenethyl Alcohol		X	X
Pogostemon Cablin Oil	X	X	X
Propylene Glycol			X
TBHQ (t-butyl hydroquinone)		X	X
Terpineol	X	X	X
Trichloromethyl Phenyl Carbinyl Acetate	X	X	X
Tromethamine		X	X

Figure 16 **Fragrance Chemicals Classified as an Irritant**

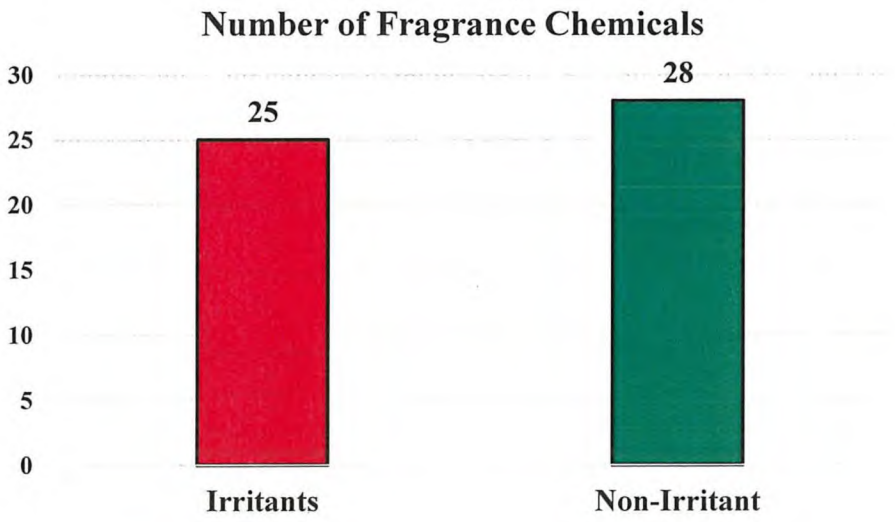


Figure 17 **Fragrance Chemicals Classified as a Skin Irritant**

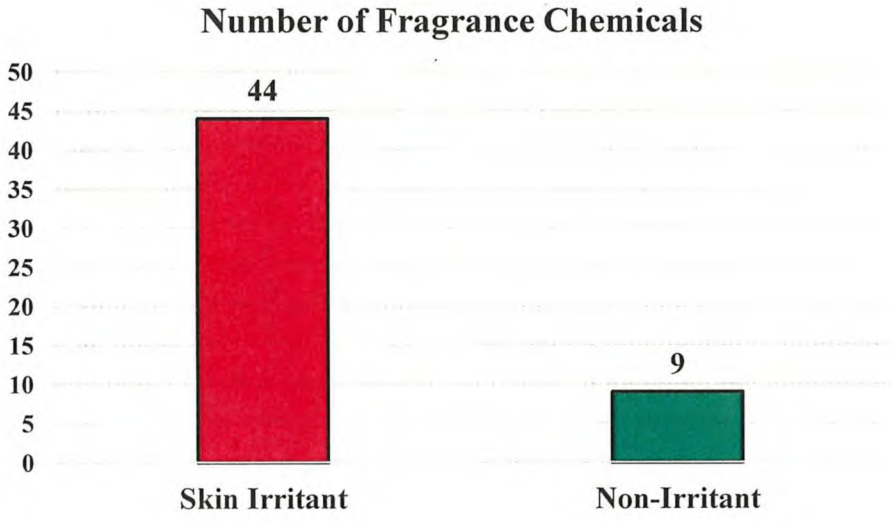
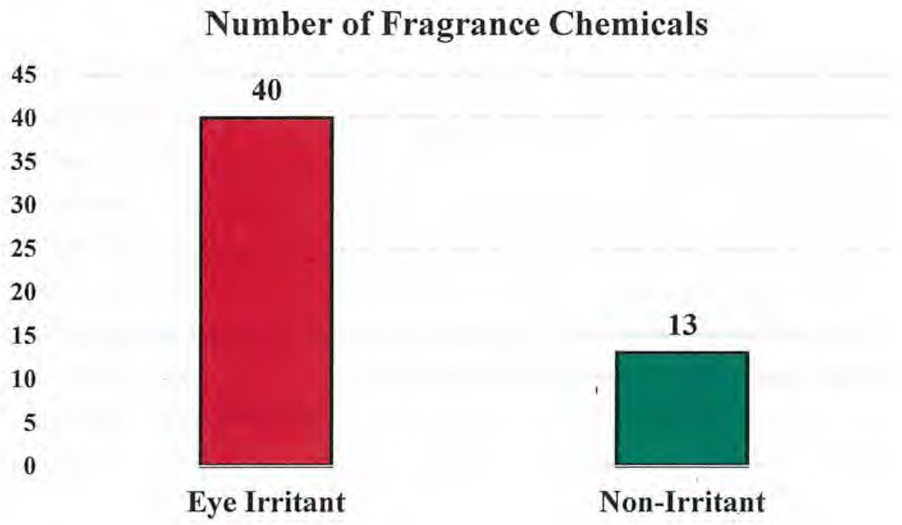


Figure 18 Fragrance Chemicals Classified as an Eye Irritant



5.5 Fragrance Chemicals Classified As Sensitizers

As described in Section 4.5, the fragrance chemicals were reviewed to identify those that are classified as sensitizers. Of the 53 fragrance chemicals in the Shower to Shower product, 16 fragrance chemicals are classified as sensitizers.

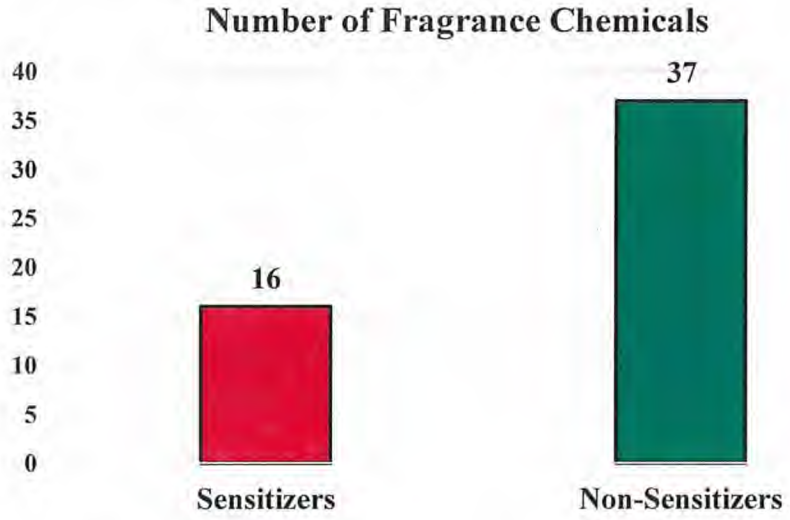
A summary of the findings is provided in Table 18 and a comparison of the number of fragrance chemicals designated as irritants, skin irritants and eye irritants are provided in Figure 19.

Table 18 Fragrance Chemicals Added to Johnson & Johnson Shower to Shower Product with Sensitization Warnings

Fragrance Chemical	Sensitization
3,7-Dimethyloct-6-en-l-ol	x
3,7-Dimethylocta-2,6-dien-1-ol	x
3-Cyclohexene-l-carboxaldehyde, 3-(4-hydroxy-4-methylpentyl)-	x
Acetic acid, anhydride, reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene	x
Acetic acid, p-tert-butylcyclohexyl ester	x
Amyl Cinnamal	x
Benzyl Benzoate	x
Benzyl Salicylate	x
Cinnamyl Alcohol	x

Fragrance Chemical	Sensitization
Commiphora Myrrha Oil	x
Coumarin	x
Eugenol	x
Geraniol	x
Isoeugenol	x
Methyl Benzoate	x
Myristica Fragrans (Nutmeg) Kernel Oil	x

Figure 19 Number of Fragrance Chemicals Classified as a Sensitization Hazard



5.6 Fragrance Chemicals Classified As Allergens and or Cause Contact Dermatitis

As described in Section 4.6, the fragrance chemicals in Shower to Shower were reviewed to identify those that are classified as allergens or with literature reports of causing contact dermatitis.

Of the 53 fragrance chemicals in the product, 16 fragrance chemicals are classified as allergens and or cause contact dermatitis.

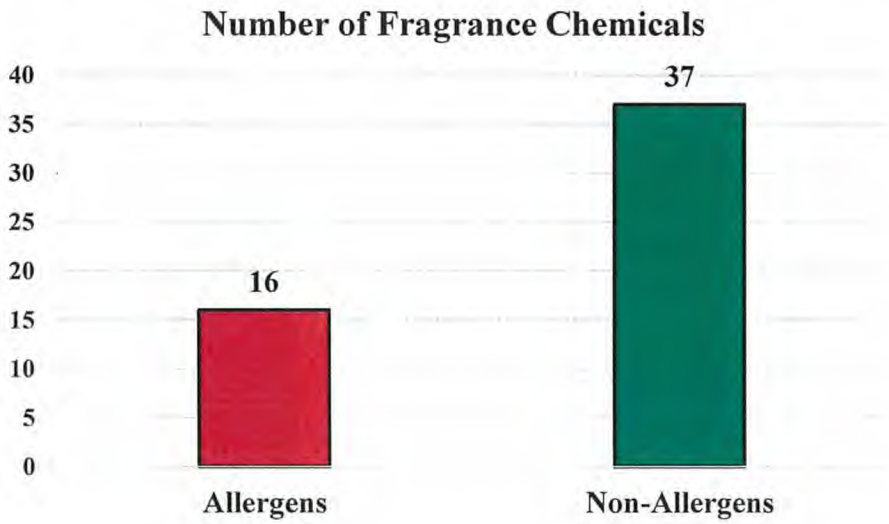
A summary of the findings is provided in Table 19 and a comparison of the number of fragrance chemicals designated as irritants, skin irritants and eye irritants are provided in Figure 20.

Table 19 Fragrance Chemicals Added to Johnson & Johnson Shower to Shower Product Classified as Allergens and or Can Cause Contact Dermatitis

Fragrance Chemical	Allergen / Contact Dermatitis
1-Benzazole	x
1-Cedr-8-en-9-ylethanone	x
3,7-Dimethyloct-6-en-l-ol	x

Fragrance Chemical	Allergen / Contact Dermatitis
3,7-Dimethylocta-2,6-dien-1-ol	x
3-Cyclohexene-l-carboxaldehyde, 3-(4-hydroxy-4-methylpentyl)-	x
Acetic acid, p-tert-butylcyclohexyl ester	x
Amyl Cinnamal	x
Benzyl Salicylate	x
Cinnamyl Alcohol	x
Commiphora Myrrha Oil	x
Cyclamen Aldehyde	x
Eugenol	x
Geraniol	x
Isoeugenol	x
Methyl Benzoate	x
TBHQ (t-butyl hydroquinone)	x

Figure 20 **Fragrance Chemicals Classified as Allergens and or Cause Contact Dermatitis**



5.7 Fragrance Chemicals with IFRA Critical Effects

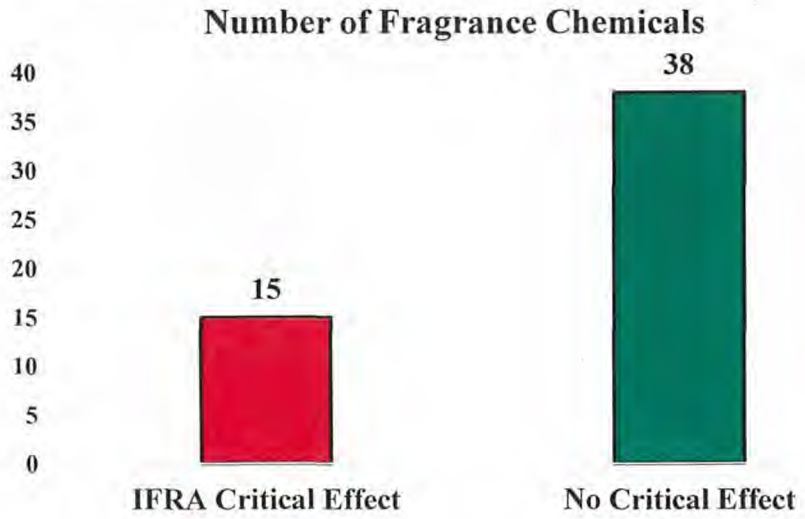
As described in Section 4.7, the fragrance chemicals in Shower to Shower were reviewed to identify those that are designated with an IFRA Critical Effect.

Of the 53 fragrance chemicals in the product, 15 fragrance chemicals have an IFRA Critical Effect. A summary of the findings is provided in Table 20 and a comparison of the number of fragrance chemicals designated with an IFRA Critical Effect is provided in Figure 21.

Table 20 Fragrance Chemicals Added to Johnson & Johnson Shower to Shower Product with IFRA Critical Effects

Fragrance Chemical	IFRA Critical Effect
2-Acetonaphthone	Phototoxicity
3,7-Dimethyloct-6-en-l-ol	Sensitization
3,7-Dimethylocta-2,6-dien-1-ol	Sensitization
3-Cyclohexene-l-carboxaldehyde, 3-(4-hydroxy-4-methylpentyl)-	Sensitization
Acetic acid, anhydride, reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene	Dermal sensitization
Amyl Cinnamal	Sensitization
Benzyl Benzoate	Sensitization
Benzyl Salicylate	Sensitization
Cinnamyl Alcohol	Sensitization
Coumarin	Sensitization
Cyclamen Aldehyde	Dermal sensitization
Eugenol	Sensitization
Geraniol	Sensitization
Isoeugenol	Sensitization
Myristica Fragrans (Nutmeg) Kernel Oil	Sensitization

Figure 21 Fragrance Chemicals with IFRA Critical Effects



5.8 Fragrance Chemicals with IFRA Category 5 Restrictions

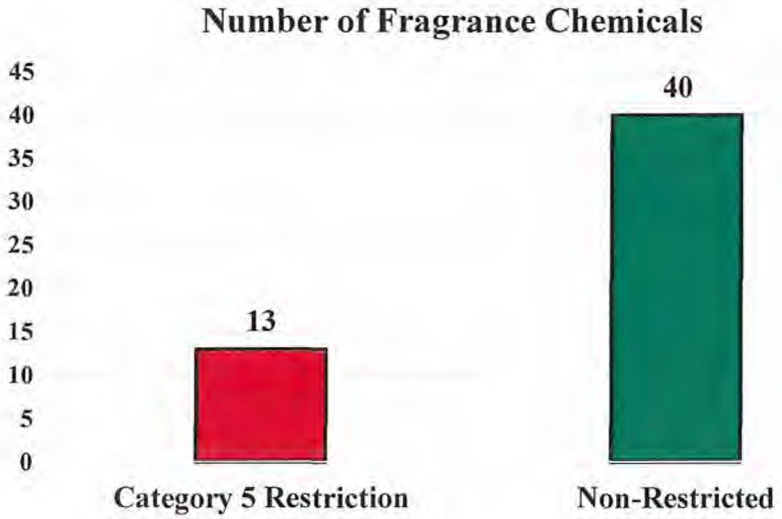
As described in Section 4.8, the fragrance chemicals in Shower to Shower were reviewed to identify those that are designated with a Category 5 Restriction.

Of the 53 fragrance chemicals in the product, 13 fragrance chemicals have a Category 5 Restriction. A summary of the findings is provided in Table 21 and a comparison of the number of fragrance chemicals designated with a Category 5 Restriction is provided in Figure 22.

Table 21 Fragrance Chemicals Added to Johnson & Johnson Shower to Shower Product with IFRA Category 5 Restriction

Fragrance Chemical	Category 5 Restriction
3,7-Dimethyloct-6-en-l-ol	7.00%
3,7-Dimethylocta-2,6-dien-1-ol	2.80%
3-Cyclohexene-l-carboxaldehyde, 3-(4-hydroxy-4-methylpentyl)-	0.20%
Acetic acid, anhydride, reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene	1.31%
Amyl Cinnamal	5.60%
Benzyl Benzoate	14.00%
Benzyl Salicylate	4.20%
Cinnamyl Alcohol	0.40%
Coumarin	0.80%
Cyclamen Aldehyde	1.40%
Eugenol	0.50%
Geraniol	2.80%
Isoeugenol	0.02%

Figure 22 Fragrance Chemicals with a Category 5 Restriction



5.9 Fragrance Chemicals with Exposure Limits

As described in Section 4.9, the fragrance chemicals in Shower to Shower were reviewed to identify those that are designated with Exposure Limits.

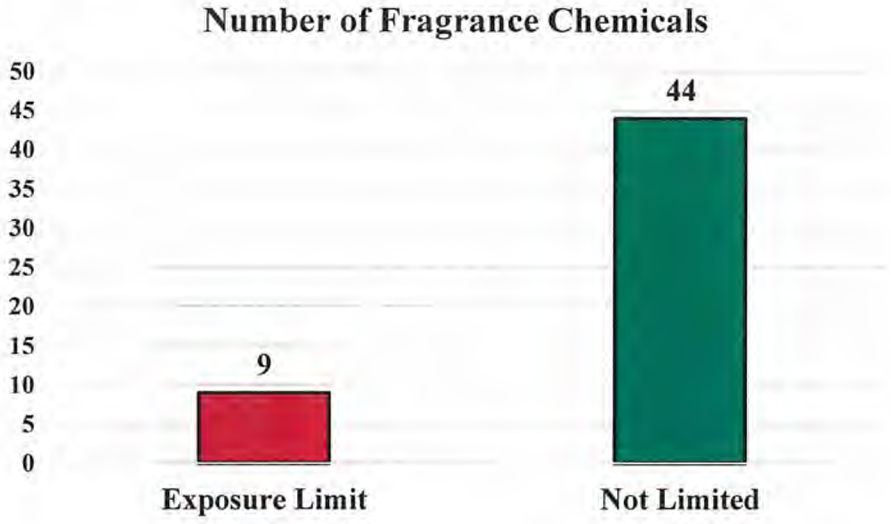
Of the 53 fragrance chemicals in the product, 9 fragrance chemicals have a Exposure Limit. A summary of the findings is provided in Table 22 and a comparison of the number of fragrance chemicals designated with an Exposure Limit is provided in Figure 23.

Table 22 Fragrance Chemicals Added to Johnson & Johnson Shower to Shower Product with Exposure Limits

Fragrance Chemical	Dermal Exposure Limit
2-Acetonaphthone	0.2% leave on the skin contact
2-Octanol, 2,6-dimethyl	Dermal Systemic Exposure in Cosmetic Products: 0.064 mg/kg/day (IFRA, 2004)
3-Cyclohexene-l-carboxaldehyde, 3-(4-hydroxy-4-methylpentyl)-	"leave on the skin contact": 1.5000 % Restriction.
3-Methylbutyl salicylate	Dermal Systemic Exposure in Cosmetic Products: 0.1042 mg/kg/day (IFRA, 2002)
3-Octanol, 3,7-dimethyl-	Dermal Systemic Exposure in Cosmetic Products: 0.0005 mg/kg/day; use level in formulae for use in cosmetics: 0.0200 %
Benzyl Salicylate	Dermal Systemic Exposure in Cosmetic Products: 0.40 mg/kg/day (IFRA, 2002)
Dihydrocitronellol	Dermal Systemic Exposure in Cosmetic Products: 0.0005 mg/kg/day

Fragrance Chemical	Dermal Exposure Limit
Methyl Benzoate	limits in the finished product for - "leave on the skin contact": 0.5000 % Recommendation.
Terpineol	Dermal Systemic Exposure in Cosmetic Products: 0.0744 mg/kg/day (IFRA, 2003)

Figure 23 Fragrance Chemicals with Exposure Limits



5.10 Fragrance Chemicals Listed on the FDA Inactive Ingredient Database (IID)

As described in Section 4.10, the fragrance chemicals in Shower to Shower were reviewed to identify those listed on the FDA IID, including those listed for topical administration (applied to the skin) and vaginal administration.

Of the 53 fragrance chemicals in the product, 11 fragrance chemicals are listed on the FDA IID, 6 are present in approved drug products for topical administration and 2 are present in an approved drug product for vaginal administration.

Table 23 Fragrance Chemicals Added to Johnson & Johnson Baby Powder Product Listed on the FDA IID

Fragrance Chemical	IID Listed	IID Listed for Topical Admin	IID Listed for Vaginal Admin
2-Propanol, 1,1'-oxybis-	x	x	
Benzyl Benzoate	x		
Diethyl Phthalate	x		
Eugenol	x		

Fragrance Chemical	IID Listed	IID Listed for Topical Admin	IID Listed for Vaginal Admin
Isopropyl Palmitate	x	x	
Myristica Fragrans (Nutmeg) Kernel Oil	x		
Phenethyl Alcohol	x	x	
Propylene Glycol	x	x	x
TBHQ (t-butyl hydroquinone)	x		x
Terpineol	x	x	
Tromethamine	x	x	

Figure 24 Fragrance Chemicals Listed on the FDA IID

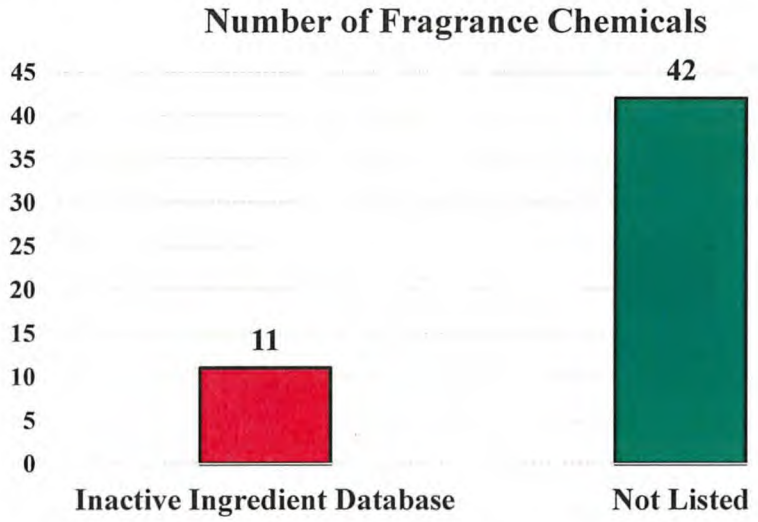


Figure 25 **Fragrance Chemicals Listed on the FDA IID for Topical Administration**

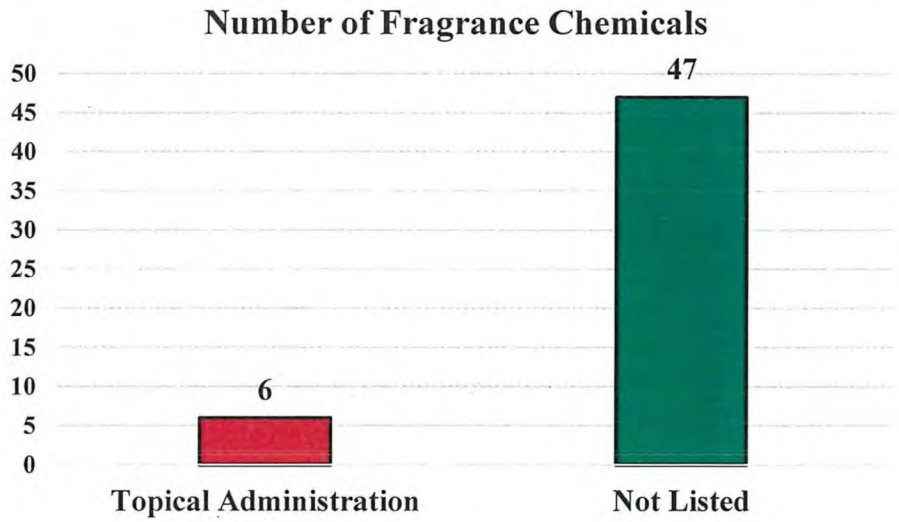
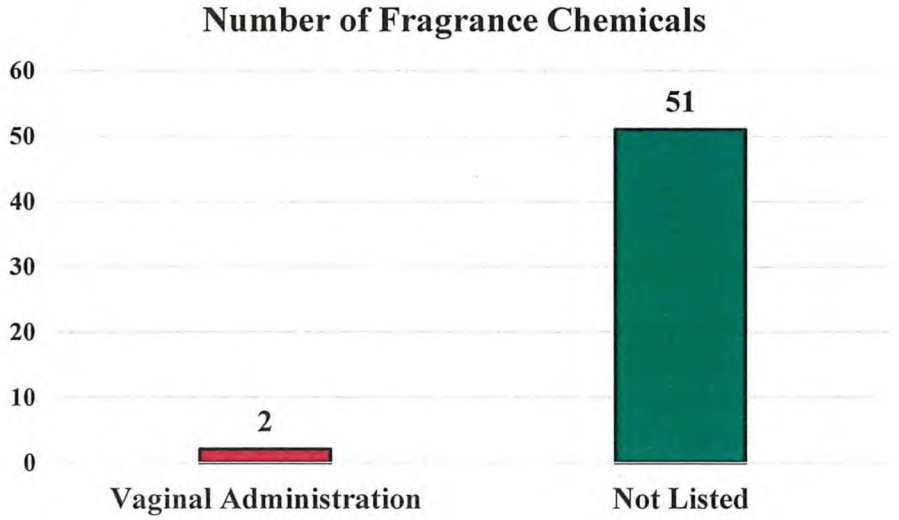


Figure 26 **Fragrance Chemicals Listed on the FDA IID for Vaginal Administration**



6 CONCLUSION AND OPINION

Based on my education, training, and experience in the fields of molecular pharmaceutics, chemistry and drug delivery, and my review of the pertinent information for this matter, I have reached the following conclusions and opinions:

6.1 The fragrance chemicals are not in compliance with governmental and industry standards

This opinion is based upon the following facts:

- Several fragrance chemicals do not have an established governmental or industry standard.
- Myroxylon Pereirae (Balsam Peru) Oil, present in Baby Powder, is prohibited as a fragrance chemical and is not permitted for use on the body.
- Benzene, ethenyl-, also known as Styrene, is not permitted for fragrance or flavor use.
- Copper Chlorophyll, a colorant, is not permitted for cosmetic use by the FDA.
- Methyl Hydrogenated Rosinate is not a fragrance, does not have an IFRA standard and is not listed by CIR.
- Para-cresol is not permitted in cosmetics according to the Cosmetic Ingredient Review Expert Panel.
- Benzophenone is no longer listed in the CFR and has no IFRA Standard.

6.2 The fragrance chemicals in Johnson and Johnson talcum powder products contribute to the inflammatory properties, toxicity, and potential carcinogenicity of the products

This opinion is based upon the following facts:

- Only 1 of the 141 fragrance chemicals in the Baby Powder product have been investigated for safety in the vagina in a product approved by the FDA.
- Only 2 of the 53 chemicals in Shower to Shower have been investigated for safety in the vagina in a product approved by the FDA.
- Several fragrance chemicals are irritants, sensitizers and allergens that can cause inflammation and oxidative stress.
- In vitro and in vivo studies have demonstrated that several fragrance chemicals have biological activity, including reproductive and developmental effects. These studies have been published in peer reviewed scientific journals.
- Four chemicals in Johnson and Johnson's Baby Powder product have been identified by the International Agency for Research on Cancer (IARC) as potential carcinogens: styrene, coumarin, eugenal and d-limone.
- Styrene has been recognized as a carcinogen by multiple governmental regulatory bodies.
- The U.S. Environmental Protection Agency considers p-cresol, also known as 4-methylphenol, to be "possibly carcinogenic".
- p-Cresol was co-carcinogenic and promoted tumors on mouse skin.

- Three fragrance chemicals added to J&J's Shower to Shower talcum product are included in the IARC monographs as possible carcinogens: benzophenone, eugenol and coumarin.
- Benzophenone was recently removed from use in foods by FDA due to histiocytic sarcoma observed in ovaries and uterus, higher incidences of kidney tumors and leukemia in animal studies, and in vivo estrogenic activity.
- Musk ketone is suspected of being a carcinogen, and has been classified as a Category 3 carcinogen by the Scientific Committee on Health and Environmental Risks (SCHER)
- Methyl Hydrogenated Rosinate is present in Baby Powder and Shower to Shower. Methyl Hydrogenated Rosinate is a film former and used to adhere the fragrance chemicals to the talcum powder.
- The safety margins of the 175 fragrance chemicals were determined for foods (oral administration) or cosmetics (topical application to the skin).
- Only 3 fragrance chemicals are present in an approved drug product administered to the vagina according to the FDA IID.
- Assuming that talcum powder migrates through the genital tract, exposure of the female reproductive organs (including vagina, endometrium, fallopian tubes, and ovaries) to talcum powder is an unintended consequence of the perineal application of Johnson's Baby Powder and Shower to Shower products
- Accordingly, in my opinion, the fragrance chemicals in the Johnson & Johnson talcum powder products contribute to the inflammatory properties, toxicity, and potential carcinogenicity of these products.

All opinions in this report are provided to a reasonable degree of scientific certainty. I reserve the right to amend or supplement this repot as more information becomes available.

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APPENDIX A: BABY POWDER FRAGRANCE CHEMICAL REVIEW

Fragrance Chemical	21 CFR	IID	Other
(d)-Limonene Carvene 5989-27-5 d-Limonene is the main constituent of orange oil and occurs in lemon, mandarin, lime, grapefruit, bergamot, neroli, petitgrain, elemi, caraway, dill, fennel, celery, erigeron and orthodon oils and a very large number of other essential oils (Gildemeister & Hoffman, 1960; Guenther, 1949).	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.60 - Synthetic flavoring substances and adjuvants. SUBCHAPTER B--FOOD FOR HUMAN CONSUMPTION 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.60 - Synthetic flavoring substances and adjuvants. SUBCHAPTER E--ANIMAL DRUGS, FEEDS, AND RELATED PRODUCTS GRAS listed for animal drugs. d-Limonene was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included d-limonene with a technological limit, except for chewing gum, in the list of artificial flavoring substances that may be added to foodstuffs without hazard to public health. The Food Chemicals Codex (1972) has a monograph on d-limonene. An extensive review of the chemistry of limonene and its derivatives has been published by Verghese (1969). **Registry of Toxic Effects of Chemical Substances (RTECS):** **DNA damage to human liver, 1 mmol/48 hour** **Reproductive Effects oral dose to mice and rats** **Tumorigenic Data** **In Vitro data on hamster ovary cells**	Approved for topical use in 3 products (2 lotions and 1 solution) at 10% w/w or 10% v/v.	PubChem https://pubchem.ncbi.nlm.nih.gov/compound/440917 H315 (100%): Causes skin irritation H317 (96.26%): May cause an allergic skin reaction R 36/38 - Irritating to skin and eyes. R 43 - May cause sensitization by skin contact. d-Limonene applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972). The Merck Index (1968) reported limonene to be a skin irritant. Limonene was well absorbed on to the skin of rats (Valette & Cavier, 1954). Irritating to the skin and is mildly irritating to the eyes. IPCS, CEC; International Chemical Safety Card on d-Limonene. (April 2005). Available from, as of February 3, 2006: http://www.inchem.org/documents/icsc/icsc/eics0918.htm Mild skin irritation may occur from exposure to limonene and oxidation products of limonene may produce **dermal sensitization**, and may have irritative and bronchoconstrictive airway effects; however, data are scant and more studies are required. Limonene has been shown to cause a **male rat-specific kidney toxicity** referred to as hyaline droplet nephropathy. Furthermore, **chronic exposure to limonene causes a significant incidence of renal tubular tumors exclusively in male rats.** **IARC (International Agency for Research on Cancer):** There is inadequate evidence in humans for the carcinogenicity of d-limonene. There is sufficient evidence in experimental animals for the carcinogenicity of d-limonene. Overall evaluation: In making its overall evaluation of the carcinogenicity to humans of d-limonene, the Working Group concluded that d-limonene

Fragrance Chemical	21 CFR	IID	Other
	https://www.cdc.gov/niosh-rtecs/GW610BC0.html European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/918.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/931.pdf		produces renal tubular tumors in male rats by a non-DNA reactive alpha-2u-globulin associated response. **Therefore, the mechanism by which d-limonene incr the incidence of renal tubular tumors in male rats is not relevant to humans. d-Limonene is not classifiable as to its carcinogenicity to humans (Group 3).** Food and Cosmetics Toxicology. Vol. 13. Pg. 825. 1975. Oyo Yakuri. Pharmacometrics. Vol. 9. Pg. 387. 1975. Risk assessment of d-limonene: an example of male rat-specific renal tumorigens. Crit Rev Toxicol. 1994:24(3):231-54. The deduction that the renal tumors induced in male rats are not relevant to human carcinogenicity in the hazard evaluation step of risk assessment completes the evaluation of human risk for d-limonene. Consequently, it can be concluded that d-limonene does not pose any carcinogenic or nephrotoxic risk to humans. NTP Toxicology and Carcinogenesis Studies of d-Limonene (CAS No. 5989-27-5) in F344/N Rats and B6C3F1 Mice (Gavage Studies). Natl Toxicol Program Tech Rep Ser. 1990 Jan;347:1-165.
1-(2.6.6-Trimethylcyclohex-2-en-1-yl)pent-1-en3-one 1-Methyl-alpha-ionone **Methyl ionone** **alpha-methyl ionone** 7779-30-8 127-42-4	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Methyl ionone was given GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1974) listed a-methyl ionone giving an ADI of 0.1 mg/kg. and included y-type methyl ionone at a level of 5 ppm in the list of artificial flavoring substances that may be added to foodstuffs without hazard to public health. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/879.pdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/61071#section=Information-Sources H315 (34.3%): Causes skin irritation [Warning Skin corrosion/irritation] H317 (72.09%): May cause an allergic skin reaction [Warning Sensitization, Skin] Contact dermatitis from methylionone fragrance. Contact Dermatitis. 1989 Jan;20(1):71-2. **IFRA RESTRICTED Dermal sensitization** http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMymqUl Irritation. Methyl ionone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). A patch test using methyl ionone at full strength for 24 hr produced no reactions in 16 subjects (Katz, 1946).

Fragrance Chemical	21 CFR	IID	Other
	http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1030/epdf		Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
1.2-Dimethoxy-4-prop-l-en-1-ylbenzene **methyl isoeugenol** (E)-methyl isoeugenol Isoeugenyl methyl ether 93-16-3 6379-72-2 6380-24-1 54349-79-0	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants GRAS listed for human foods (oral) Methyl isoeugenol was given GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1974) listed methyl isoeugenol, giving an ADI of 5 mg/kg. The Food Chemicals Codex has a monograph on methyl isoeugenol. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2010.1899/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2012.2678/epdf	Not Listed	PubChem: https://pubchem.ncbi.nlm.nih.gov/compound/637776#section=CAS **H317 (86.67%): May cause an allergic skin reaction [Warning Sensitization, Skin]** **S 24/25 - Avoid contact with skin and eyes.** **RTECS** **In Vitro/Hamster, ovary** **In Vitro Toxicity Studies: Cell viability (mitochondrial reductase assays): MTT, XTT, MTS, WSTs assays etc.** **DNA Damage to human Liver** https://www.cdc.gov/niosh-rtecs/CZ6ACFC0.html Food and Cosmetics Toxicology. Vol. 13, Pg. 865, 1975. Irritation. Methyl isoeugenol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was irritating (Keating, 1972). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972). Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
1.5-Dimethyl-1-vinylhex-4-en-I-yl benzoate **Linalyl Benzoate** CAS Registry Number 126-64-7 Linalyl benzoate is found in herbs and spices. Linalyl benzoate is found in ylang-ylang and tuberose essential oils and mushrooms.	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. GRAS listed for human foods (oral) Linalyl benzoate was given GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1974) included linalyl benzoate at a level of 1 ppm in the list of artificial flavoring substances that may be added to foodstuffs without	Not Listed	PubChem: https://pubchem.ncbi.nlm.nih.gov/compound/Linalyl_benzoate#section=BioAssay-Results H319 (100%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] Linalyl benzoate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Moreni, 1973). Food and Chemical Toxicology 41 (2003) 977–981 Food and Cosmetics Toxicology. Vol. 14, Pg. 461, 1976.

Fragrance Chemical	21 CFR	IID	Other
	hazard to public health. The Food Chemicals Codex has a monograph on linalyl benzoate. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/835.pdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1025/epdf		Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ol **borneol** **Isoborneol** Isocamphol CAS Registry Number 124-76-5 10334-13-1	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. GRAS listed for human foods (oral)	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/Isoborneol Xi - Irritant R 36/37/38 - Irritating to eyes, respiratory system, and skin. R 42/43 - May cause sensitization by inhalation and skin contact. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/743.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/746.pdf **Enhanced the transdermal penetration of drugs** https://www.ncbi.nlm.nih.gov/pubmed/26635061 Food and Cosmetics Toxicology. Vol. 17, Pg. 531, 1979. Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
1-acetonaphthone **alpha-naphthyl methyl ketone** a-Methyl Naphthyl Ketone 941-98-0	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. GRAS listed for human foods (oral) European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/330.pdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/13663#section=Top H315 (11.59%): Causes skin irritation [Warning Skin corrosion/irritation] H317 (80.69%): May cause an allergic skin reaction [Warning Sensitization, Skin] H319 (11.16%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H335 (10.3%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation] Food and Chemical Toxicology. Vol. 20, Pg. 755, 1982.

Fragrance Chemical	21 CFR	IID	Other
	http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/810.pdf		Sporn, A., Schoebesch, I., Marin, Victoria, Panaitescu, Elena & Runcanu, Lucia (1963). The toxicity of butyl acetate, methyl naphthyl ketone, and ionone. Igiena 12, 437. Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
1-Benzazole **Indole** [2] Benzopyrrole CAS Registry Number 120-72-9 Reported to occur in over two dozen essential oils including neroli oil and in the oils extracted from the flowers of Jasminum grandiflorum, bitter orange and Jasminum odoratissimium L. It occurs naturally in human feces and has an intense fecal smell. At very low concentrations, however, it has a flowery smell, and is a constituent of many flower scents (such as orange blossoms) and perfumes.	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Indole was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) included indole in the list of admissible artificial flavoring substances at a level of 1 ppm. The Food Chemicals Codex has a monograph on indole. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/372.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/792.pdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/798 H311 - Toxic in contact with skin H315 - Causes skin irritation R 37/38 - Irritating to respiratory system and skin. R 41 - Risk of serious damage to eyes. Yakugaku Zasshi. Journal of Pharmacy. Vol. 94. Pg. 1620. 1974. American Industrial Hygiene Association Journal. Vol. 23. Pg. 95. 1962. Klinische Wochenscrift. Vol. 35. Pg. 504. 1957. The compound was tested externally on the eyes of rabbits, and, according to the degree of injury observed after 24 hours, rated on a scale of 1 to 10. The most severely injurious substances have been rated 10. Indole rated 8 on rabbit eyes. Grant, W.M. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher. 1986., p. 1040
1-Cedr-8-en-9-ylethanone acetyl cedrene methyl cedryl ketone vertofix (IFF)	**Could not locate in 21 CFR** **Could not locate an IFRA Standard** **Not Listed by CIR**	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/107065#section=Top **H317 (94.26%): May cause an allergic skin reaction [Warning Sensitization, Skin]** **Mucous membrane irritant (eye)** **R 36/38 - Irritating to skin and eyes.**

[2] Indole in Phenoxy Ethanol was replaced by Indole in Benzzyl Benzoate in April, 2014 according to Exhibit 3 "CHANGES TO JOHNSON'S BABY POWDER FRAGRANCE INGREDIENTS"

Fragrance Chemical	21 CFR	IID	Other
CAS Registry Number 32388-55-9			**Allergic contact dermatitis** from the synthetic fragrances Lyral and acetyl cedrene in separate underarm deodorant preparations. Contact Dermatitis. 1994 Nov;31(5):288-90. https://www.ncbi.nlm.nih.gov/pubmed/7867324 Food Chem Toxicol. 2013 Dec;62 Suppl 1:S152-66 Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
1-Methyl-1-(4-methylcyclohex-3-en-1-yl)ethyl acetate Terpinene 4-acetate **Terpinyl acetate** alpha-Terpineol acetate CAS Registry Number 80-26-2 alpha-Terpineol acetate is found in cardamom.	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Terpinyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. It was listed by the Council of Europe (1970), with an ADI of **1 mg/kg**, and is the subject of a Food Chemicals Codex monograph.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/111037 Xi - Irritant R 36/38 - Irritating to skin and eyes. Food & Cosmetics Tox 1974 12:999 page 699 Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
1-Phenylethyl acetate methyl benzyl acetate Methylbenzyl acetate, mixed o-,m-,p-. **styralyl acetate** **methylphenylcarbinyl acetate** gardenol alpha-Methylbenzyl acetate 29759-11-3 93-92-5 Found in cloves and gardenia flower	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Methylphenylcarbinyl acetate was given GRAS status by FEMA (1965) and is approved by the FDA for food use. The Food Chemicals Codex has a monograph on methylphenylcarbinyl acetate.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/1-Phenylethyl_acetate#section=Top Food and Chemical Toxicology 50 (2012) S388–S393 Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
2-Acetonaphthone beta-naphthyl methyl ketone	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION	Not listed	https://pubchem.ncbi.nlm.nih.gov/compound/7122#section=Top **H315 (11.04%): Causes skin irritation [Warning Skin corrosion/irritation]**

Fragrance Chemical	21 CFR	IID	Other
1-naphthalen-2-ylethanone Methyl b-naphthyl ketone 93-08-3	§ 172.515 - Synthetic flavoring substances and adjuvants. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/330.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/810.pdf		**R 36/38 - Irritating to skin and eyes.** **IFRA Use Restriction: Phototoxicity** http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl **limits in the finished product for - "leave on the skin contact": 0.2000 % Restriction.** **In Vitro Human Androgen Receptor Activity** Irritation. A patch test using b-methyl naphthyl ketone at full strength for 24 hr produced one irritation reaction in 24 human subjects (Katz, 1946). Medizin und Ernaehrung. Vol. 8, Pg. 244, 1967. Oser, B.L., Carson, S., Oser, M., 1965. Toxicological tests on flavoring matters. Food Cosmet. Toxicol. 3, 563–569 Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
2-Isopropenyl-5-methylcyclohexanol **Isopulegol** p-menth-8-en-3-ol 7786-67-6 89-79-2	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Isopulegol was given GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1974) included isopulegol in the list of artificial flavoring substances that may be added temporarily to foodstuffs without hazard to public health. The Food Chemicals Codex has a monograph on isopulegol	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/24585#section=Top **R 36/38 - Irritating to skin and eyes.** **H315 (82.31%): Causes skin irritation [Warning Skin corrosion/irritation]** **H319 (80.82%): Causes serious eye irritation [Warning Serious eye damage/eye irritation]** Acute toxicity. The acute oral LD 50 in rats was reported as 1.03 ± 0.10 ml/kg and the **acute dermal L D 50 in rabbits as approximately 3 ml/kg** (Lynch, 1971). Irritation. Isopulegol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was severely irritating (Lynch, 1971). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971). Food and Cosmetics Toxicology. Vol. 13, Pg. 823, 1975. Food and Chemical Toxicology 97 (2016) S129eS135

Fragrance Chemical	21 CFR	IID	Other
			Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
2-Isopropyl-5-methylcyclohexanol **MENTHOL** 89-78-1 1490-04-6 15356-70-4 491-01-0 Menthol is an organic compound made synthetically or obtained from peppermint or mint oils with flavoring and local anesthetic properties. When added to pharmaceuticals and foods, menthol functions as a fortifier for peppermint flavors. It also has a **counterirritant effect on skin and mucous membranes**, thereby producing a local analgesic or anesthetic effect. Penetration Enhancer	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). 310: NEW DRUGS § 310.531 - Drug products containing active ingredients offered over-the-counter (OTC) for the treatment of boils. § 310.544 - Drug products containing active ingredients offered over-the-counter (OTC) for use as a smoking deterrent. § 310.545 - Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses. 341: COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTIASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE § 341.14 - Antitussive active ingredients. § 341.40 - Permitted combinations of active ingredients. § 341.70 - Labeling of OTC drug products containing ingredients that are used for treating concurrent symptoms (in either a single-ingredient or combination drug product). § 341.74 - Labeling of antitussive drug products. § 341.85 - Labeling of permitted combinations of active ingredients. 346: ANORECTAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE § 346.16 - Analgesic, anesthetic, and antipruritic active ingredients. § 346.50 - Labeling of anorectal drug products.	An inactive ingredient in oral, buccal, topical, and sublingual drugs. Approved in 31 drug products for oral, buccal, topical and inhalation routes of admin. Not present in any approved drugs for vaginal administration.	https://pubchem.ncbi.nlm.nih.gov/compound/1254 **Xi - Irritant** **R 37/38 - Irritating to respiratory system and skin.** **R 41 - Risk of serious damage to eyes.** Irritation. Menthol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was **mildly irritating** (Levenstein, 1973). Absorption can occur from topical use. Dermal Systemic Exposure in Cosmetic Products: 0.0074 mg/kg/day (IFRA, 2004) use level in formulae for use in cosmetics: 0.2900 % H315 (97.9%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (83.01%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] Menthol may cause allergic reactions (e.g. contact dermatitis, flushing, and headache) in certain individuals. All studied isomers of menthol are, if applied undiluted, moderately irritating to skin. OECD; Sreening Information Data Set (SIDS) Inital Assessment Report for SIDS Initial Assessment Meeting (SIAM) 16 Menthols(CASN 2216-51-5, 15356-60-2, 89-78-1, 1490-04-6) p. 9 (2003). Available from, as of June 2, 2015: A severe eye irritant. Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience. Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 2297 Food and Cosmetics Toxicology. Vol. 2, Pg. 327, 1964. European Food Safety Authority (EFSA) reference(s):

Fragrance Chemical	21 CFR	IID	Other
	358: MISCELLANEOUS EXTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE § 358.720 - Permitted combinations of active ingredients. 172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). 14: PUBLIC HEARING BEFORE A PUBLIC ADVISORY COMMITTEE § 14.100 - List of standing advisory committees.		http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/331.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/855.pdf Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
2-Phenylethyl 3-methylbutanoate **phenethyl isovalerate** isovaleric acid, phenethyl ester 140-26-1	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Phenylethyl isovalerate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). It was included by the Council of Europe (1970) in the list of admissible artificial flavoring substances at a level of 5 ppm (except for chewing gum), and is the subject of a Food Chemicals Codex monograph.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/8792#section=Top Xi - Irritant R 36/38 - Irritating to skin and eyes. Food and Cosmetics Toxicology. Vol. 12. Pg. 961. 1974. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/216.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/710.pdf Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
2-Phenylethyl formate **phenethyl formate** formic acid, 2-phenylethyl ester 104-62-1	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Phenylethyl formate was granted GRAS status by FEMA (1965) and is approved by	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/7711 Xi - Irritant R 36/38 - Irritating to skin and eyes. H317 (100%): May cause an allergic skin reaction [Warning Sensitization, Skin] Food Chem Toxicol. 2012, Sep; 50 Suppl 2:S425-9

Fragrance Chemical	21 CFR	IID	Other
Found in bilberry, blackberry, coffee and tea.	the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed phenylethyl formate, giving an ADI of 5 mg/kg.		Food and Cosmetics Toxicology. Vol. 12, Pg. 959, 1974. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/216.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/710.pdf
2-Phenylethyl phenylacetate phenethyl phenyl acetate **phenethyl phenylacetate** CAS Number: 102-20-5 Found in linden.	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Phenylethyl phenylacetate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included it at a level of 10 ppm in the list of artificial flavoring substances that may be added to foodstuffs without hazard to public health. The Food Chemicals Codex (1972) has a monograph on phenylethyl phenylacetate.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/7601 Xi N - Irritant. Dangerous for the environment. R 36/38 - Irritating to skin and eyes. Food and Cosmetics Toxicology. Vol. 2, Pg. 327, 1964. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/216.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/710.pdf Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
2-Propanol, 1,1'-oxybis- **Dipropylene glycol** 1-(1-Hydroxypropoxy)propan-1-ol 1,1'-dimethyldiethylene glycol CAS Number 25265-71-8 110-98-5	175: INDIRECT FOOD ADDITIVES: ADHESIVES AND COMPONENTS OF COATINGS § 175.105 - Adhesives. § 175.320 - Resinous and polymeric coatings for polyolefin films. 176: INDIRECT FOOD ADDITIVES: PAPER AND PAPERBOARD COMPONENTS § 176.170 - Components of paper and paperboard in contact with aqueous and fatty foods. § 176.180 - Components of paper and paperboard in contact with dry food. § 176.200 - Defoaming agents used in coatings. 177: INDIRECT FOOD ADDITIVES: POLYMERS § 177.2420 - Polyester resins, cross-linked.	Approved in transdermal and buccal drug products up to 49 mg.	https://pubchem.ncbi.nlm.nih.gov/compound/8087#section=Toxicity **H315 (97.83%): Causes skin irritation [Warning Skin corrosion/irritation]** **H319 (100%): Causes serious eye irritation [Warning Serious eye damage/eye irritation]** **S 24/25 - Avoid contact with skin and eyes.** **Solvent** **Cosmetic Use:** **masking agents, perfuming agents, solvents** **viscosity controlling agents** A skin and eye irritant.

Fragrance Chemical	21 CFR	IID	Other
	178: INDIRECT FOOD ADDITIVES: ADJUVANTS, PRODUCTION AIDS, AND SANITIZERS § 178.3910 - Surface lubricants used in the manufacture of metallic articles. **No IFRA Standard** **Registry of Toxic Effects of Chemical Substances** https://www.cdc.gov/niosh-rtecs/UB860C68.html **Skin and Eye Irritation and References**		Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 2805 "Toxicology of Drugs and Chemicals." Deichmann, W.B., New York, Academic Press, Inc., 1969Vol. -, Pg. 731, 1969. Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ CIR: https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr193.pdf
3-(5,5,6-Trimethylbicyclo[2.2.1]hept-2-yl)cyclohexanol Isobornyl cyclohexanol **ISOCAMPHYL CYCLOHEXANOL** (MIXED ISOMERS) sandal hexanol indisan (IFF) cyclohexanol, (2,2,3-trimethylnorbornanyl)- (mixed isomers) 3407-42-9 80748-58-9 Found in sandalwood oil.	**Could not locate in 21 CFR.** **Isocamphyl cyclohexanol (mixed isomers) is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the Food Chemicals Codex.** **No IFRA Standard** **Not Listed by CIR**	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/103005#section=Top H315 (95.2%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (34.69%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] BioAssay Results: 25 Active Irritation. Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion it was moderately irritating (Moreno, 1975). Tested at 20% in petrolatum it produced irritant reactions in two out of 25 human subjects in a 48-hr closed-patch test (Epstein, 1975). Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
3,7-Dimethyloct-6-en-1-ol **Citronellol** [3]	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/8842 Xi N - Irritant, Dangerous for the environment.

[3] Citronellol 850 was replaced by CITRONELLOL 950 SYN in February, 2010 according to Exhibit 3 "CHANGES TO JOHNSON'S BABY POWDER FRAGRANCE INGREDIENTS"

Fragrance Chemical	21 CFR	IID	Other
106-22-9 Citronellol has been found in nature, and it has been reported in about 70 essential oils.	§ 172.515 - Synthetic flavoring substances and adjuvants. Citronellol was given GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1974) listed citronellol, giving an ADI of 0.25 mg/kg. The Food Chemicals Codex has a monograph on citronellol and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for citronellol, giving a conditional ADI of 0-0.25 mg/kg. ADI revised to 0-0.5 mg/kg bw in 2003. **IFRA Use Restriction due to Sensitization** http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/616.pdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2010.1402/epdf		H315 (95.35%): Causes skin irritation [Warning Skin corrosion/irritation] H317 (99.55%): May cause an allergic skin reaction [Warning Sensitization, Skin] H319 (64.43%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Citronellol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was **moderately irritating** (Moreno, 1973). A patch test using a 1% concentration of citronellol in acetone gave a **positive reaction in subjects allergic to citronella oil** (Keil, 1947). 5 Active BioAssay Results Adult male volunteers with no known allergic reactions were patch-tested on their back for 48 hr with 32% citronellol. After 48 hr, patches were removed and the skin was cleaned of any residual test material. Moderate irritation was observed. A patch test using a 1% concentration of citronellol in acetone gave a **positive reaction in subjects allergic to citronella oil**. Journal of Scientific and Industrial Research, Section C: Biological Sciences. Vol. 21, Pg. 342, 1962. Food and Cosmetics Toxicology. Vol. 13, Pg. 757, 1975. In vitro human skin penetration of geraniol and citronellol. Dermatitis. 2010 Jan-Feb;21(1):41-8. Low potential for skin penetration by in vitro test. Sensitization to 26 fragrances to be labelled according to current European regulation. Results of the IVDK and review of the literature. Contact Dermatitis. 2007 Jul;57(1):1-10. Skin penetration of terpenes from essential oils and topical vehicles. Planta Med. 2006 Mar;72(4):311-6.

Fragrance Chemical	21 CFR	IID	Other
			Citronellol applied in a hydrogel penetrated into all skin layers in a total amount of 25 microg/cm (2), while no penetration into viable skin layers after application of an oily solution was noted. Only citronellol permeated into the acceptor medium.
3,7-Dimethylocta-2,6-dien-1-yl acetate **GERANYL ACETATE** trans-3,7-dimethyl-2,6-octadien-1-yl ethanoate 105-87-3	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.60 - Synthetic flavoring substances and adjuvants. 172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.60 - Synthetic flavoring substances and adjuvants. Geranyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) listed geranyl acetate, giving an ADI of 5 mg/kg. The Food Chemicals Codex has a monograph on geranyl acetate and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for the ester giving a conditional ADI of 0.5 mg/kg. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2004.108/epdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/616.pdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/1549026 Moderately Toxic: Probable Oral Lethal Dose (Human) 0.5-5 G/KG, between 1 OZ & 1 PINT (OR 1 LB) FOR 70 KG PERSON (150 LB). /GERANIOL/ Gosselin, R.E., H.C. Hodge, R.P. Smith, and M.N. Gleason. Clinical Toxicology of Commercial Products, 4th ed. Baltimore: Williams and Wilkins, 1976., p. II-168 Xi – Irritant R 36/38 - Irritating to skin and eyes. H315 (15.29%): Causes skin irritation [Warning Skin corrosion/irritation] H317 (15.29%): May cause an allergic skin reaction [Warning Sensitization, Skin] /HUMAN EXPOSURE STUDIES/ In human patch test, geraniol at 32% concentration was **severely irritating** and geranyl acetate mildly irritating. MOTOYOSKI ET AL; COSMET TOILETRIES 94(8) 41 (1979) National Toxicology Program Reports Carcinogenesis Studies of Food Grade Geranyl Acetate (71% Geranyl acetate, 29% Citronellyl Acetate) in F344/N Rats and B6C3F1 Mice (Gavage Study). Technical Report Series No. 252 (1987) NIH Publication No. 88-2508 U.S. Department of Health and Human Services, National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709 Not considered carcinogenic. 2 Active BioAssay Results Food and Cosmetics Toxicology. Vol. 2, Pg. 327, 1964. Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/

Fragrance Chemical	21 CFR	IID	Other
3,7-Dimethylocta-2,6-dien-1-yl benzoate **geranyl benzoate** trans-3,7-dimethyl-2,6-octadien-1-yl benzoate CAS Number: 94-48-4	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Geranyl benzoate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) included geranyl benzoate in the list of artificial flavoring substances not admissible at present because of insufficient data. The Food Chemicals Codex has a monograph on geranyl benzoate. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1025/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1081/epdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/5353011 Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ **S 24/25 - Avoid contact with skin and eyes** **H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation]** **H319 (100%): Causes serious eye irritation [Warning Serious eye damage/eye irritation]** **Skin Use Recommendation: limits in the finished product for - "leave on the skin contact": 0.5000 % Recommendation.** Food and Cosmetics Toxicology. Vol. 12, Pg. 887, 1974.
3,7-Dimethylocta-2,6-dien-1-yl phenylacetate GERANYL PHENYLACETATE CAS Number: 102-22-7	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Geranyl phenylacetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) included geranyl phenylacetate in the list of admissible artificial flavoring substances at a level of 5 ppm (except for chewing gum). The Food Chemicals Codex has a monograph on geranyl phenylacetate.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/5366044#section=Top Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 12, Pg. 895, 1974.
3-Methyl-1H-indole **SKATOLE** **83-34-1**	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/6736#section=Top Acute toxicity. The acute oral LD 50 value in rats was reported as 3-45 ± 0-372 g/kg and the acute dermal LD 50 value in rabbits as <5g/kg (McGee, 1974). The ip L D 50 of skatole in mice was determined as 175 mg/kg, the toxic effects being seen as **macroscopic and microscopic lesions in the liver, spleen,**

Fragrance Chemical	21 CFR	IID	Other
It occurs naturally in feces (it is produced from tryptophan in the mammalian digestive tract), beets, and coal tar, and has a strong fecal odor. In low concentrations it has a flowery smell and is found in several flowers and essential oils, including those of orange blossoms, jasmine, and Ziziphus mauritiana.	Skatole was given GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1974) included skatole at a level of 1 ppm in the list of artificial flavoring substances that may be added to foodstuffs without hazard to public health. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/372.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/792.pdf **Registry of Toxic Effects of Chemical Substances (RTECS)** https://www.cdc.gov/niosh-rtecs/NM55730.html **Cytogenetic Analysis: ovary/hamster, 1.4 mmol/L/3H (+/-enzymatic activation step) EMMUEG 40, 1, 2002** **DNA Adduct in several species including human**		**kidneys and lungs** (Kader, Zaki & Moustafa, 1961), and subsequently as > 2 mmol/kg (Shinoda, Ohta, Hino & Akaboshi, 1974). A dose of 4 mmol skatole/kg injected sc was toxic to mice (Mirsky, Diengott & Perisutti, 1957). **Xi – Irritant** **H315 (96.3%): Causes skin irritation** **H319 (96.3%): Causes serious eye irritation** **4 Active Bioassay Results** Food and Cosmetics Toxicology. Vol. 14, Pg. 863, 1976. **Toxicol Sci. 2009 Nov;112(1):59-67** **3-Methylindole is mutagenic and a possible pulmonary carcinogen** Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 14, Pg. 863, 1976. Archives of Environmental Contamination and Toxicology. Vol. 14, Pg. 111, 1985.
3-Methyl-5-(2,2,3-trimethylcyclopent-3-en-1-yl)pentan-2-ol Sandalore sandal pentanol sandalore (Givaudan) dersantol 65113-99-7	**Could Not Locate** **Could not locate an IFRA Standard**	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/Sandalore **Xi – Irritant** **H319 (16.31%): Causes serious eye irritation** **R 36/37/38 - Irritating to eyes, respiratory system, and skin.** S 26 - In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. **Listed in Toxic Substances Control Act (TSCA) Chemical Substance Inventory: Substance name index to the initial inventory United States. Environmental Protection Agency. Office of Toxic Substances, 1979 Volume 3, page 1544** Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/

Fragrance Chemical	21 CFR	IID	Other
3-Phenylpropan-1-ol 3-Phenyl-1-propanol 3-phenyl propyl alcohol benzene propanol 122-97-4	FDA PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/247.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/733.pdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/Benzenepropanol **Xi – Irritant** **R 36/38 - Irritating to skin and eyes.** **S 24/25 - Avoid contact with skin and eyes.** **S 26 - In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.** **H315 - Causes skin irritation** **H319 - Causes serious eye irritation** In a multicenter study, 218 fragrance sensitive patients with proven contact dermatitis were patch tested. Reactions (0.9%) in fragrance sensitive patients were observed with 3-phenylpropanol at 5% in petrolatum. An in vitro percutaneous absorption study of 3-phenyl-1-propanol, across human skin was conducted using a diffusion cell. Permeable across skin. Repeat skin test in 50 humans showed no reactions. Bhatia SP et al: 49(2): S246-51 (2011). https://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel+122-97-4 **1 Active BioAssay Result** Food and Cosmetics Toxicology. Vol. 17, Pg. 893, 1979. Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
4-(2,5,6,6-Tetramethylcyclohex-2-en-1-yl)but-3-en-2-one alpha-irone 6-Methyl-oc-ionone 79-69-6	FDA PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. a-Irone was granted GRAS status by FEMA (1965) and is approved by the FDA for food	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/5371002 Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Irritation. a-Irone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was **mildly irritating** (Shelanski, 1972). **S 24 - Avoid contact with skin.**

Fragrance Chemical	21 CFR	IID	Other
	use. The Council of Europe (1974) listed a-irone, giving an ADI of 0.1 mg/kg. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1030/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2015.4172/epdf		**S 25 - Avoid contact with eyes.** **IFRA Use Restriction Due to Sensitization** http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl **Dermal Systemic Exposure in Cosmetic Products: 0.0055 mg/kg/day (IFRA, 2001)** **1 Active BioAssay Result** Food Chem Toxicol. 2007;45 Suppl 1:S272-5
4-(2,6,6-Trimethylcyclohex-2-en-1-yl)but-3-en-2-one **alpha-ionone** cyclocitrylidenacetone. 127-41-3	FDA PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. Both a and ß-ionone were granted GRAS status by FEMA (1965) and are approved by the FDA for food use. The Council of Europe (1974) listed a- and ß-ionone, giving ADIs of 0.1 mg/kg for both. The Food Chemicals Codex has monographs on a- and ß-ionone and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published monographs and specifications for both isomers, giving conditional ADIs of 0-0.1 mg/kg. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/879.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/910.pdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/5282108 **Xi – Irritant** **R 36/38 - Irritating to skin and eyes.** **S 24/25 - Avoid contact with skin and eyes.** **R 42/43 - May cause sensitization by inhalation and skin contact.** **H334 (60.42%): May cause allergy or asthma symptoms or breathing difficulties if inhaled [Danger Sensitization, respiratory]** **Respiratory sensitisation (Category 1), H334** **Dermal Systemic Exposure in Cosmetic Products: 0.05 mg/kg/day (IFRA, 2002)** **IFRA Use Restricted due to Sensitization** http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl alpha-Ionone was found to be a **moderate skin irritant.** Lalko J et al; Food Chem Toxicol 45 Suppl 1: S235-40 (2007) /**GENOTOXICITY**/ Genotoxicity of 9 flavor materials, including alpha-ionone, was evaluated using CH cell line B241 in culture stages between the 5th and 8th stages. One day after seeding, exponentially growing cells were exposed to each chemical in DMSO for 24 hr. The cells were further incubated for another 24 hr without the chemicals. **alpha-ionone at 25 mM concentration caused significant increases in chromosome aberrations.** Lalko J, et al; Food Chem Toxicol 45 Suppl 1: S235-40 (2007)

Fragrance Chemical	21 CFR	IID	Other
			Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
4-Methylphenyl 2-methylpropanoate P-Cresyl isobutyrate p-tolyl isobutyrate 103-93-5	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. p-Cresyl isobutyrate was given GRAS status by FEM A (1965) and is approved by the FDA for food use. The Council of Europe (1974) included p-cresyl isobutyrate at a level of 0.15 ppm in the list of artificial flavoring substances that may be added to foodstuffs without hazard to public health. The Food Chemicals Codex (1972) has a monograph on p-cresyl isobutyrate. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.1990/epdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/711.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/393.pdf **Registry of Toxic Effects of Chemical Substances (RTECS)** https://www.cdc.gov/niosh-rtecs/NQ535020.html	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/7685#section=Top Xi - Irritant R 36/37/38 - Irritating to eyes, respiratory system, and skin. Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ p-Cresyl isobutyrate applied full strength to the intact or abraded skin of rabbits for 24 hr under occlusion was mildly irritating (Levenstein, 1974). Tested on human subjects by a 48-hr occluded-patch test at 4% in petrolatum, the material was not irritating (Kligman, 1974). Food and Cosmetics Toxicology. Vol. 13, Pg. 773, 1975.
4-Methylphenyl octanoate P-Cresyl octanoate para-cresyl caprylate p-tolyl octanoate p-tolyl caprylate	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/43046#section=Top **R 22 - Harmful if swallowed.** **R 36/38 - Irritating to skin and eyes.** Food and Cosmetics Toxicology. Vol. 16, Pg. 697, 1978.

Fragrance Chemical	21 CFR	IID	Other
59558-23-5	p-Cresyl phenylacetate was given GRAS status by FEM A (1965) and is approved by the FDA for food use. The Council of Europe (1974) included p-cresyl phenylacetate at a level of 5 ppm in the list of artificial flavoring substances that may be added to foodstuffs without hazard to public health.		Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
4-Methylphenyl phenylacetate para-cresyl phenyl acetate p-tolyl phenylacetate P-Cresyl Phenylacetate 101-94-0	FDA PART 172 – FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. p-Cresyl phenylacetate was given GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1974) included p-cresyl phenylacetate at a level of 5 ppm in the list of artificial flavoring substances that may be added to foodstuffs without hazard to public health.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/60997#section=Top **S 24/25 - Avoid contact with skin and eyes.** Acute toxicity, Oral (Category 4), H302 Irritation. p-Cresyl phenylacetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Food and Cosmetics Toxicology. Vol. 13, Pg. 775, 1975. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/711.pdf Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
5-Isopropenyl-2-methylcyclohex-2-en-1-one **Carvone** limonen-6-one 99-49-0 43205-82-9 33375-08-5 Found in anise.	FDA PART 182 – SUBSTANCES GENERALLY RECOGNIZED AS SAFE Subpart A--General Provisions Sec. 182.60 Synthetic flavoring substances and adjuvants. Carvone was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) listed carvone, giving an ADI of 1.25 mg/kg. The Food Chemicals Codex has a monograph on carvone, and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for carvone, giving an ADI of 1.25 mg/kg.	Present in one drug product (sublingual tablet) for oral administration at 0.081 mg.	https://pubchem.ncbi.nlm.nih.gov/compound/521267#section=Molecular-Formula https://pubchem.ncbi.nlm.nih.gov/compound/7439#section=Top Food and Cosmetics Toxicology. Vol. 2, Pg. 327, 1964. *Journal of the American Pharmaceutical Association. Scientific Edition*. Vol. 46, Pg. 77, 1957. H302 (50.79%): Harmful if swallowed **H315 (99.37%): Causes skin irritation** **H317 (92.11%): May cause an allergic skin reaction** **IFRA Use Restriction due to Sensitization** http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl

Fragrance Chemical	21 CFR	IID	Other
	European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2014.3806/epdf		Allergic contact dermatitis from carvone in hair conditioners. Dermatitis. 2010 Mar-Apr;21(2):116-7. The sensitizing potential of l-carvone has been considered low, but it has occasionally caused contact allergy in users of spearmint toothpaste and chewing gum.
8-Cyclohexadecen-1-one musk dec-8-enone globanone (Symrise) animusk 3100-36-5 5365-06-0	**Could not locate** **IFRA indicates not for flavor or food use** **Could not locate an IFRA standard** **Not listed by CIR**	Not listed	https://pubchem.ncbi.nlm.nih.gov/compound/534634 **H315 (68.75%): Causes skin irritation** **H315 (68.75%): Causes skin irritation [Warning Skin corrosion/irritation]** Food Chem Toxicol. 2011 Dec;49 Suppl 2:S109-11. Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ **Very little safety / tox info available**
Acetic acid, phenylmethyl ester Benzyl Acetate 140-11-4 Occurs in jasmine, apple, cherry, guava fruit and peel, wine grape, white wine, tea, plum, cooked rice, Bourbon vanilla, naranjila fruit (Solanum quitoense), Chinese cabbage and quince.	FDA PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. Benzyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) listed benzyl acetate, giving an ADI of 5 mg/kg. The Food Chemicals Codex has a monograph on benzyl acetate, and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specification for benzyl acetate, giving an unconditional ADI of 0.5 mg/kg body weight in man. European Food Safety Authority (EFSA) reference(s):	Approved in one drug product for oral administration (elixir). Amount approved is unknown.	https://pubchem.ncbi.nlm.nih.gov/compound/benzyl_acetate **Cosmetic Uses:** **masking agents** **perfuming agents** **solvents** **Xi – Irritant** **H315: Causes skin irritation [Warning Skin corrosion/irritation]** **H319: Causes serious eye irritation [Warning Serious eye damage/eye irritation]** **H336: May cause drowsiness or dizziness [Warning Specific target organ toxicity, single exposure; Narcotic effects]** **H370: Causes damage to organs [Danger Specific target organ toxicity, single exposure]** **H372: Causes damage to organs through prolonged or repeated exposure [Danger Specific target organ toxicity, repeated exposure]** **H373: Causes damage to organs through prolonged or repeated exposure [Warning Specific target organ toxicity, repeated exposure]** **Irritating to skin, eyes, respiratory tract.**

Fragrance Chemical	21 CFR	IID	Other
	http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/296.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/637.pdf **Registry of Toxic Effects of Chemical Substances (RTECS)** https://www.cdc.gov/niosh-rtecs/AF4D7038.html **DNA Damage** **Mutations**		**Budavari, S. (ed.). The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc., 1989., p. 176** **Effects of Long Term Exposure: Defats the skin, which may cause dryness or cracking. The substance may have effects on the kidneys.** http://www.ilo.org/dyn/icsc/showcard.display?p_version=2&p_card_id=1331 Not classified as a carcinogen 7 Active BioAssay Results Mutat Res. 1994 Apr 1:306(1):107-9. Benzyl acetate: from mutagenic carcinogen to non-mutagenic non-carcinogenic in 7 years? Natl Toxicol Program Tech Rep Ser. 1993 Sep;431:1-285. NTP Toxicology and Carcinogenesis Studies of Benzyl Acetate (CAS No. 140-11-4) in F344/N Rats and B6C3F1 Mice Feed Studies). Food and Cosmetics Toxicology. Vol. 11. Pg. 875. 1973. Journal of Pharmacology and Experimental Therapeutics. Vol. 84. Pg. 358. 1945. Food Chem Toxicol. 2012 Sep;50 Suppl 2:S363-84. IARC Monogr Eval Carcinog Risks Hum. 1999;71 Pt 3:1255-64. Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
Aldehyde C-7 **Heptanal** oenanthic aldehyde CAS Number: 111-71-7 Found in the essential oils of ylang-ylang, clary sage, California lemon, bitter orange.	FDA PART 172 – FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. Aldehyde C-7 was given GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1974)	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/8130 **Xi – Irritant** **H315 (99.71%): Causes skin irritation [Warning Skin corrosion/irritation]** **H319 (92.08%): Causes serious eye irritation [Warning Serious eye damage/eye irritation]** Skin, Eye, and Respiratory Irritations

Fragrance Chemical	21 CFR	IID	Other
rose and hyacinth.	included aldehyde C-7 at a level of 5 ppm in the list of artificial flavoring substances that may be added to foodstuffs without hazard to public health. The Food Chemicals Codex has a monograph on aldehyde C-7. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/688.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/934.pdf		Clayton, G. D. and F. E. Clayton (eds.). Patty's Industrial Hygiene and Toxicology: Volume 2A, 2B, 2C: Toxicology. 3rd ed. New York: John Wiley Sons, 1981-1982., p. 2633 Skin Sensitization in Guinea Pig SHELL OIL CO: Toxicology of Ethylene Oxide Derivatives: The Skin Sensitizing Potential of Heptanal (Final Report) with Attachment and Cover Letter Dated 12/02/91; 01/01/82; EPA Doc. No. 86-920000444; Fiche No. OTS0534500 3 Active BioAssay Results In studies of the blood, lung tissues and bone marrow of rabbits given 01 or 0-5 ml/kg/day on 5 days/wk for 4 wk, erythrocyte aldolase activity decreased and disturbances in respiratory tissue occurred (Esposito & Nicolini, 1962). Organic defence indexes (serum bactericidal activity and properdin level) in rabbits were lowered by im injection of 0-1 ml/kg/day for 7 consecutive days, a dose corresponding to the therapeutic antitumour dose (Diomede-Fresa & Fumarola, 1960). Aldehyde C-7 applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was **very irritating** (Moreno, 1974). Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
Alpha-Isomethyl Ionone cetone alpha (Givaudan) 127-51-5	FDA PART 172 – FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. Methyl ionone was given GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1974) listed á-methyl ionone giving an ADI of 0-1 mg/kg, and included y-type methyl ionone at a level of 5 ppm in the list of artificial flavoring substances that may be added to foodstuffs without hazard to public health.		https://pubchem.ncbi.nlm.nih.gov/compound/alpha-Cetone Methyl ionone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was **moderately irritating** (Moreno, 1973). Xi – Irritant H315 (80.27%): Causes skin irritation [Warning Skin corrosion/irritation] H317 (90.98%): May cause an allergic skin reaction [Warning Sensitization, Skin] H319 (68.2%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] 4 Active BioAssay Results IFRA Use Restricted due to Dermal sensitization

Fragrance Chemical	21 CFR	IID	Other
	European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/879.pdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1030/epdf		http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl Dermal Systemic Exposure in Cosmetic Products: 0.33 mg/kg/day (IFRA, 2001) Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 2, Pg. 327. 1964.
Amyl Cinnamal **AMYL CINNAMIC ALDEHYDE** alpha-amyl cinnamaldehyde alpha-pentylcinnamaldehyde 122-40-7 alpha-Amyl cinnamaldehyde has a jasmine-like odor and is a widely used synthetic fragrance & suspected allergen. *It is used in allergenic testing.*	FDA PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. Amyl cinnamic aldehyde was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) included amyl cinnamic aldehyde (α-amyl cinnamaldehyde). in the list of admissible artificial flavoring substances at a level of 1 ppm. The Food Chemicals Codex has a monograph on amyl cinnamic aldehyde. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/880.pdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1032/epdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/1712058#section=Top IFRA Use Restricted due to Sensitization http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl **Xi – Irritant** **R 36/37/38 - Irritating to eyes, respiratory system, and skin.** **R 43 - May cause sensitisation by skin contact.** **H317 (98.8%): *May cause an allergic skin reaction* [Warning Sensitization, Skin]** **Skin sensitisation (Category 1), H317** **A severe skin irritant.** **Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 251** Cinnamic aldehyde allergy. Contact Dermatitis. 1975;1(2):108-11. Positive patch test reactions to 2% cinnamic aldehyde were obtained from 2.8% of 34 males and 9.1% of 55 females. Fragrance contact dermatitis: a worldwide multicenter investigation (Part II). PMID 11380544: Contact dermatitis 2001 Jun;44(6):344-6 Sensitivity to alpha-amylcinnamic aldehyde (alpha-AcAld) is apparently uncommon, but, like allergy to alpha-amylcinnamic alcohol (alpha-AcAlc), it often accompanies allergy to the perfume in Mycolog cream. Although alpha-AcAlc is a known

Fragrance Chemical	21 CFR	IID	Other
			ingredient, alpha-AcAld is not. However, gas-liquid chromatographic analysis shows alpha-AcAld to be present. Of fourteen persons sensitive to either chemical, ten reacted to both. Of these, one man and three women were markedly sensitive, and all **three women had chronic recalcitrant vulvar eczema.** That condition might have been the cause as well as the result of sensitization, but reexposure to a suspected product reproduced the eruption in both persons tested. Its use with other potent sensitizers, e.g., ethylenediamine, to treat irritations and chronic eczemas in an area of high absorption may partly explain development of allergy to a relatively weak sensitizer. Guin JD, Haffley P: J Am Acad Dermatol 8 (1): 76-80 (1983) 3 Active BioAssay Results Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 2, Pg. 327, 1964.
Anisaldehyde p-methoxybenzaldehyde **ANISIC ALDEHYDE** 123-11-5 Found in American cranberry, anise oil, fennel and vanilla.	FDA PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. Anisic aldehyde was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) listed anisic aldehyde giving an ADI of 1 mg/kg. The Food Chemicals Codex has a monograph on anisic aldehyde. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/296.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/637.pdf	Not listed	https://pubchem.ncbi.nlm.nih.gov/compound/31244 Cosmetic Uses: masking agents perfuming agents IFRA Use Restricted due to Sensitization http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl Xi - Irritant R 36/38 - Irritating to skin and eyes. Acute toxicity, dermal (Category 5), H313 Skin corrosion/irritation (Category 3), H316 3 Active BioAssay Results Food and Cosmetics Toxicology. Vol. 12, Pg. 823, 1974. Anisic aldehyde applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Fragrance Chemicals of Concern Present on the IFRA List 2015:

Fragrance Chemical	21 CFR	IID	Other
			https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
Benzaldehyde 100-52-7 Benzaldehyde is occasionally found as a volatile component of urine. Benzaldehyde is an aromatic aldehyde used in cosmetics as a denaturant, a flavoring agent, and as a fragrance. Currently used in only seven cosmetic products, its highest reported concentration of use was 0. 5% in perfumes. Benzaldehyde is a generally regarded as safe (GRAS) food additive in the United States and is accepted as a flavoring substance in the European Union. Because Benzaldehyde rapidly metabolizes to Benzoic Acid in the skin, the available dermal irritation and sensitization data demonstrating no adverse reactions to Benzoic Acid were considered supportive of the safety of Benzaldehyde. Benzaldehyde is absorbed through skin and by the lungs, distributes to all well-perfused organs, but does not accumulate in any specific tissue type.	FDA PART 172 – FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. Benzaldehyde was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) listed benzaldehyde giving an ADI of 4 mg/kg. The Food Chemicals Codex has a monograph on benzaldehyde and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications, giving an unconditional ADI of 0-5 mg/kg. **Registry of Toxic Effects of Chemical Substances (RTECS)** https://www.cdc.gov/niosh-rtecs/CU42C1D8.html **Tumorigenic: Neoplastic by RTECS criteria** **It may cause contact dermatitis. It was positive in sister chromatid exchange assay with human lymphocytes from healthy non-smoking donors. Benzaldehyde was found to induce formation of stable DNA-protein cross-links in cultured human lymphoma cells. Benzaldehyde was found to lack significant activity against most human tumor cells tested.** European Food Safety Authority (EFSA) reference(s):	In one drug product for oral administration at 0.6 mg / mL.	https://pubchem.ncbi.nlm.nih.gov/compound/240 Benzaldehyde is absorbed through skin and by the lungs, distributes to all well-perfused organs, but does not accumulate in any specific tissue type. After being metabolized to benzoic acid, conjugates are formed with glycine or glucuronic acid, and excreted in the urine. Andersen A; Int J Toxicol 25 Suppl 1:11-27 (2006) R 36/38 - Irritating to skin and eyes. H312 (52%): Harmful in contact with skin H315 (48%): Causes skin irritation H319 (50%): Causes serious eye irritation H317 - May cause an allergic skin reaction IFRA Use Restricted due to Sensitization http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl 12 Active BioAssay Results Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ **Irritation:** Benzaldehyde applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on two different panels of human subjects (Kligman, 1973). Thomas (1958) reported, however, that benzaldehyde, like other aldehydes and aldehyde-containing essential oils, was strongly irritating to the skin. **Sensitization:** In patch tests using 5% benzaldehyde in vaseline, positive reactions were observed in ten of 100 patients. Positive reactions occurred in patients with sensitivity to benzoic acid or vanillin (Hjorth, 1961).

Fragrance Chemical	21 CFR	IID	Other
Benzaldehyde was not considered a carcinogenic risk to humans. http://www.hmdb.ca/metabolites/HMDB0006115	http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/296.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/637.pdf		Two animals were dosed with 100 microliter of test substance in the eye and observed for 7 days. The test substance was slightly irritating to the rabbit eye in this test. European Chemicals Agency (ECHA): Registered Substances. Benzaldehyde (CAS Number: 100-52-7) (EC Number: 202-860-4) (Last updated: December 29, 2015). Available from, as of April 25, 2016: http://echa.europa.eu/ The present study shows that intensive administration of benzyl derivatives used as flavoring agents **may have a significant genotoxic effects.** Demir E et al: Food Chem Toxicol 46 (3): 1034-41 (2008) **Inactivation of glutathione peroxidase by benzaldehyde.** PMID 8975763; Toxicology and applied pharmacology 1996 Dec:141(2):389-93
Benzaldehyde, 2-hydroxy- Salicylaldehyde o-hydroxybenzaldehyde 90-02-8 Found in common buckwheat and cinnamon.	FDA PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/296.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/637.pdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/6998 R 21/22 - Harmful in contact with skin and if swallowed. R 36/38 - Irritating to skin and eyes. **H341 (48.8%): Suspected of causing genetic defects [Warning Germ cell mutagenicity]** 3 Active BioAssay Results Food and Cosmetics Toxicology. Vol. 17, Pg. 903, 1979. Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
Benzene, 1,2-dimethoxy- ortho-dimethyl hydroquinone Veratrole 1,2-DIMETHOXYBENZENE 91-16-7	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. European Food Safety Authority (EFSA) reference(s):	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/7043 11 Active BioAssay results Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/

Fragrance Chemical	21 CFR	IID	Other
1, 2-Dimethoxybenzene is found in corn, cheeses, grapes and asparagus.	http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/417.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/639.pdf		
Benzene, 1,3-dimethoxy- meta-dimethyl hydroquinone m-dimethoxybenzene 151-10-0 Found in mushrooms.	FDA PART 172 – FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/417.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/639.pdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/1_3-Dimethoxybenzene#section=Top Xi – Irritant H312 (50%): Harmful in contact with skin [Warning Acute toxicity, dermal] H315 (50%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (50%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] Journal of the American Pharmaceutical Association. Scientific Edition. Vol. 46. Pg. 185. 1957. FOOD CHEM TOXICOL 21:707-719.1983 Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
Benzene, ethenyl- Styrene vinylbenzene 100-42-5 FDA filed a food additive petition (FAP 6A4817) proposing that we amend § 172.515 to no longer provide for the use of styrene as a synthetic flavoring substance and adjuvant in food because the use has been abandoned.	FDA PART 172 – FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. Several other approved uses with polymers for indirect food contact A colorless, toxic liquid with a strong aromatic odor. It is used to make rubbers, polymers and copolymers, and polystyrene plastics. Present in cranberry, bilberry, currants, grapes, vinegar, parsley, milk and	Not Listed **Styrene has been implicated as reproductive toxicant, neurotoxicant, or carcinogen in vivo or in vitro.** http://www.hmdb.ca/metabolites/HMDB0006236	https://pubchem.ncbi.nlm.nih.gov/compound/7501 **R 36/38 - Irritating to skin and eyes.** **H315 (100%): Causes skin irritation** **H319 (99.9%): Causes serious eye irritation** **H361 (31.97%): *Suspected of damaging fertility or the unborn child* [Warning Reproductive toxicity]** **H372 (71%): Causes damage to organs through prolonged or repeated exposure** The absorption of styrene in humans proceeds by all routes, but mainly through the respiratory tract. Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons. New York, N.Y. (2001).. p. V4 313

Fragrance Chemical	21 CFR	IID	Other
FDA published a final rule granting the petition to no longer authorize the use of styrene as a synthetic flavoring substance and adjuvant in food because its use under § 172.515 has been permanently and completely abandoned. https://www.federalregister.gov/documents/2018/10/09/2018-21807/food-additive-regulations-synthetic-flavoring-agents-and-adjuvants	dairy products, whisky, cocoa, coffee, tea, roasted filberts and peanuts. Flavoring ingredient. Polymers are used in ion-exchange resins in food processing. Indirect food additive arising from adhesives, coatings and packaging materials Styrene, also known as vinyl benzene, is a colorless oily liquid that evaporates easily and has a sweet smell, although high concentrations confer a less pleasant odor. Styrene is the precursor to polystyrene and several copolymers. Low levels of styrene occur naturally in plants as well as a variety of foods such as fruits, vegetables, nuts, beverages, and meats. **Registry of Toxic Effects of Chemical Substances (RTECS)** http://webapp1.dlib.indiana.edu/virtual_disk_library/index.cgi/5678550/FID2757/nioshdbs/rtecs/wl381378.htm **Agency for Toxic Substances and Disease Registry** https://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=74 **Immediately Dangerous to Life or Health Concentrations (IDLH)** https://www.cdc.gov/niosh/idlh/100425.html **On Prop 65 List of Carcinogens**		**Styrene, it has been observed, crosses the placenta.** **Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 313 vol 4** **Styrene partitions to human fat and concentrations therein account for approximately 8% of the inhaled compound. The human elimination halftime for styrene from adipose tissue is 2 to 4 days.** **American Conference of Governmental Industrial Hygienists. Documentation of the TLV's and BEI's with Other World Wide Occupational Exposure Values. CD-ROM Cincinnati, OH 45240-1634 2005., p. 5** Dermal absorption of styrene is considered to be minimal. However, skin absorption does occur /at a rate of 0.06 mg/sq cm/hr/. Percutaneous absorption of styrene is incr if skin is injured. Sullivan, J.B., Krieger G.R. (eds). Clinical Environmental Health and Toxic Exposures. Second edition. Lippincott Williams and Wilkins, Philadelphia, Pennsylvania 1999., p. 1155 pharmacokinetic (PBPK) model describing the distribution and metabolism of styrene Csanady GYA et al; Arch Toxicol 68 (3): 143-57 (1994) **Toxic by all routes (ie, inhalation, ingestion, and dermal contact), exposure to this colorless-to-yellow, sweet-smelling liquid may occur from its presence in the manufacture and use of plastics, synthetic rubber, resins, coatings, paints, floor waxes, adhesives, putty, metal cleaners, autobody fillers, and varnishes.** https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@rn+@rel+100-42-5 **Confirmed carcinogen** **Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 3313** **inhalation, skin absorption, ingestion, skin and/or eye contact** https://www.cdc.gov/niosh/npg/npgd0571.html

Fragrance Chemical	21 CFR	IID	Other
			Exposure Limits **NIOSH REL** **TWA 50 ppm (215 mg/m3) ST 100 ppm (425 mg/m3)** **OSHA PEL** **TWA 100 ppm C 200 ppm 600 ppm (5-minute maximum peak in any 3 hours)** **Target Organs** **Eyes, skin, respiratory system, central nervous system, liver, reproductive system** Fragrance Chemicals on the European Union Endocrine Disruptors Priority List https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-endocrine-disruptors-priority-list/ Fragrance chemicals classified as carcinogens by the IARC Monographs, Volumes 1–113 https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-carcinogens-iarc-monographs/ Fragrance chemicals on the ChemSec SIN List https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-on-the-chemsec-sin-list/
Benzeneacetic acid Phenylacetic Acid Acetic acid, phenyl- a-Toluic acid 103-82-2 51146-16-8	FDA PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. Phenylacetic acid was given GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1974) included phenyl acetic acid at a level of 25 ppm in the list of artificial flavoring substances that may be added to foodstuffs without hazard to public health. The Food Chemicals Codex (1972) has a monograph on phenylacetic acid.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/999#section=Molecular-Formula **Xi – Irritant** **R 36/37/38 - Irritating to eyes, respiratory system, and skin.** **Skin irritation (Category 2), H315** **Eye irritation (Category 2A), H319** **Specific target organ toxicity - single exposure (Category 3), Respiratory system, H335** **Reproductive toxicity (Category 2), H361** Food and Cosmetics Toxicology. Vol. 13, Pg. 901, 1975. Food Chem Toxicol. 2005 Aug;43(8):1179-206. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/638.pdf

Fragrance Chemical	21 CFR	IID	Other
	Registry of Toxic Effects of Chemical Substances (RTECS) https://www.cdc.gov/niosh-rtecs/AJ251430.html Reproductive Effects		http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/710.pdf Phenylacetic acid... /is/ rapidly absorbed from human buccal tissues or membranes. National Research Council. Drinking Water & Health Volume 1. Washington, DC: National Academy Press, 1977., p. 754 /LABORATORY ANIMALS: **Developmental or Reproductive Toxicity**/ In teratogenic study with rats, administration of phenylacetic acid on 12th day of embryogenesis affected body weight, retarded skeletal ossification, and caused embryos to be resorbed at twice rate of controls. Dosage was 0.2% of LD50, or 3.2 mg/kg. National Research Council. Drinking Water & Health Volume 1. Washington, DC: National Academy Press, 1977., p. 754 Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
Benzeneacetic acid, methyl ester Methyl phenyl acetate Methyl a-toluate 101-41-7 Methyl phenylacetate is found in cocoa and cocoa products.	FDA PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. Methyl phenylacetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. It was included by the Council of Europe (1970) in the list of temporarily admissible artificial flavoring substances, and is the subject of a Food Chemicals Codex (1972) monograph. The Joint FAO/WHO Expert Committee on Food Additives (1968) was unable to arrive at an ADI for methyl phenylacetate because of a lack of toxicological data.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/7559 **Xi – Irritant** **R 36/38 - Irritating to skin and eyes.** Acute toxicity, Oral (Category 5), H303 Acute toxicity, dermal (Category 5), H313 **Skin corrosion/irritation (Category 3), H316** Food and Cosmetics Toxicology. Vol. 12, Pg. 941, 1974. Methyl phenylacetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was very slightly irritating (Moreno, 1974). Food and Cosmetics Toxicology. Vol. 12, Pg. 941, 1974. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/216.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/710.pdf

Fragrance Chemical	21 CFR	IID	Other
Benzeneacetic acid, phenylmethyl ester Benzyl Phenylacetate 102-16-9	FDA PART 172 – FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. Benzyl phenylacetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) included benzyl phenylacetate in the list of admissible artificial flavoring substances at a level of 5 ppm. The Food Chemicals Codex (1972) has a monograph on benzyl phenylacetate.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/60999#section=Synonyms 3 Active BioAssay Results European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/296.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/835.pdf Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
Benzoic acid, 2,4-dihydroxy-3,6-dimethyl-, methyl ester Methyl atrarate Methyl 3-Methylorsellinate veramoss (IFF) evernyl (Givaudan) 4707-47-5	**Could not locate in CFR or IFRA Standard.** Listed as an EU flavor for foods. The natural compound atraric acid is an antagonist of the human androgen receptor inhibiting cellular invasiveness and prostate cancer cell growth. PMID 18627423: Journal of cellular and molecular medicine 2009 Aug:13(8B):2210-23 European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/296.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/637.pdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/78435 Xi – Irritant H315 (95.83%): Causes skin irritation H319 (95.83%): Causes serious eye irritation H335 (95.83%): May cause respiratory irritation Skin irritation (Category 2), H315 Eye irritation (Category 2A), H319 Specific target organ toxicity - single exposure (Category 3), Respiratory system, H335 10 Active BioAssay Results Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
Benzoic acid, 2-hydroxy-, 2-methylpropyl ester Isobutyl Salicylate	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/6873 R 36/37/38 - Irritating to eyes, respiratory system, and skin.

Fragrance Chemical	21 CFR	IID	Other
87-19-4	Isobutyl salicylate was given GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1974) included isobutyl salicylate at a level of 5 ppm in the list of artificial flavoring substances that may be added to foodstuffs without hazard to public health. The Food Chemicals Codex (1972) has a monograph on isobutyl salicylate.		Isobutyl salicylate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1973). Adams T.B., Cohen S.M., Doull J., Feron V.J., Goodman J.I., Marnett L.J., Munro I.C., Portoghese P.S., Smith R.L., Waddell W.J. and Wagner B.M. 2005. The FEMA GRAS assessment of hydroxyl- and alkoxy-substituted benzyl derivatives used as flavor ingredients. Food and Chemical Toxicology. 43, 1241. Food and Cosmetics Toxicology. Vol. 13, Pg. 813, 1975. Safety evaluation of certain food additives and contaminants prepared by the fifty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Food Additives Series No. 48, 2002 Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
Benzoic acid, 2-hydroxy-, ethyl ester ethyl salicylate 118-61-6 Ethyl salicylate is present in feijoa fruit, raspberry, tomato, various spirits, red wine, mountain papaya and cape gooseberry.	FDA PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. Ethyl salicylate is found in alcoholic beverages. Ethyl salicylate is present in feijoa fruit, raspberry, tomato, various spirits, red wine, mountain papaya and cape gooseberry. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/296.pdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/8365 D - Dermatologicals D01 - Antifungals for dermatological use R 36/37/38 - Irritating to eyes, respiratory system, and skin. 1 Active BioAssay Result IFRA Use Restriction: maximum skin levels for fine fragrances: 0.1400 % and are based on the assumption that the fragrance mixture is used at 20% in a consumer product (IFRA Use Level Survey). (IFRA, 2002) Food and Cosmetics Toxicology. Vol. 16, Pg. 751, 1978. Food Chem Toxicol. 2007;45 Suppl 1:S397-401 American Journal of Physiology. Vol. 13, Pg. 331, 1905. Dermal Systemic Exposure in Cosmetic Products: 0.0002 mg/kg/day (IFRA, 2002) **The estrogenic potential of salicylate esters and their possible risks in foods and cosmetics.** **Toxicol Lett. 2012 Mar 7;209(2):146-53**

Fragrance Chemical	21 CFR	IID	Other
			https://www.ncbi.nlm.nih.gov/pubmed/22197706 Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
Benzyl Alcohol Phenylmethyl alcohol 100-51-6	FDA PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. FDA PART 175 -- INDIRECT FOOD ADDITIVES: ADHESIVES AND COMPONENTS OF COATINGS Subpart B--Substances for Use Only as Components of Adhesives Sec. 175.105 Adhesives. FDA PART 175 -- INDIRECT FOOD ADDITIVES: ADHESIVES AND COMPONENTS OF COATINGS Subpart C--Substances for Use as Components of Coatings Sec. 175.300 Resinous and polymeric coatings. FDA PART 177 -- INDIRECT FOOD ADDITIVES: POLYMERS Subpart B--Substances for Use as Basic Components of Single and Repeated Use Food Contact Sec. 177.1210 Closures with sealing gaskets for food containers. FDA PART 73 -- LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION Subpart B--Drugs Sec. 73.1001 Diluents in color additive mixtures for drug use exempt from certification.	Present in 111 drug products, admin routes include injection, otic, dental, epidural, extracorporeal, IM-IV, Institial, oral, nasal, topical and vaginal. Vaginal use up to 1%. Ulesfia (benzyl alcohol) lotion is indicated for the topical treatment of head lice infestation in patients 6 months of age and older. It is used as a local anesthetic and to reduce pain associated with Lidocaine injection.	https://pubchem.ncbi.nlm.nih.gov/compound/244#section=Top H312 (17.85%): Harmful in contact with skin [Warning Acute toxicity, dermal] H319 (23.23%): Causes serious eye irritation R 43 - May cause sensitisation by skin contact. Eye irritation (Category 2A), H319 The undiluted material applied to the depilated skin of guinea-pigs for a period of 24 hr caused moderately strong primary irritation (Treon, 1963). Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/296.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/637.pdf Found in jasmine, hyacinth, ylang-ylang oils and at least two dozen other essential oils. Acceptable daily intakes were established by the World Health Organization at 5 mg/kg for Benzyl Alcohol. Benzyl Alcohol could be used safely at concentrations up to 5%, but that manufacturers should consider the nonimmunologic phenomena when using benzyl alcohol in cosmetic formulations designed for infants and children.

Fragrance Chemical	21 CFR	IID	Other
	Benzyl alcohol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) listed benzyl alcohol, giving an ADI of 5 mg/kg. The Food Chemicals Codex (1972) and the National Formulary (1970) have monographs on benzyl alcohol and another extensive monograph has been provided by Browning (1965). Registry of Toxic Effects of Chemical Substances (RTECS) https://www.cdc.gov/niosh-rtecs/DN3010B0.html		
Benzyl Benzoate phenylmethyl benzoate 120-51-4	573: FOOD ADDITIVES PERMITTED IN FEED AND DRINKING WATER OF ANIMALS § 573.210 - Benzoic acid. 310: NEW DRUGS § 310.545 - Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses. 172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. 175: INDIRECT FOOD ADDITIVES: ADHESIVES AND COMPONENTS OF COATINGS § 175.105 - Adhesives. Benzyl benzoate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) listed benzyl benzoate, giving an ADI of 5 mg/kg. The Food Chemicals Codex (1972) has a monograph on benzyl benzoate. Registry of Toxic Effects of Chemical Substances (RTECS)	Present in 5 drug products. Route of admin includes injection and oral. Benzyl benzoate is one of the older preparations used to treat scabies. It is also used to treat lice infestation of the head and body. Benzyl benzoate is not the treatment of choice for scabies due to its irritant properties.	https://pubchem.ncbi.nlm.nih.gov/compound/benzyl_benzoate R 43 - May cause sensitisation by skin contact. S 25 - Avoid contact with eyes. Benzyl benzoate is a primary skin irritant (Schwartz, Tulipan & Birmingham, 1957), but used as a 2 0% emulsion in the treatment of scabies in 1000 persons it produced no dermatitis (Graham, 1943). Four cases of dermatitis have been attributed to benzyl benzoate by Dougherty (1945). Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Cosmetic Uses: antimicrobial agents perfuming agents solvents Food and Cosmetics Toxicology. Vol. 11, Pg. 1015, 1973. Journal of Pharmacology and Experimental Therapeutics. Vol. 93, Pg. 26, 1948.

Fragrance Chemical	21 CFR	IID	Other
	https://www.cdc.gov/niosh-rtecs/DG401640.html		
Benzyl Salicylate 118-58-1	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Benzyl salicylate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) included benzyl salicylate in the list of admissible artificial flavoring substances at a level of 2 ppm. The Food Chemicals Codex (1972) has a monograph on benzyl salicylate. Benzyl salicylate is found in cloves. Benzyl salicylate is isolated from essential oils e. g. Dianthus caryophyllus. Populus. Primula species **The estrogenic potential of salicylate esters and their possible risks in foods and cosmetics.** **Toxicol Lett. 2012 Mar 7;209(2):146-53** https://www.ncbi.nlm.nih.gov/pubmed/22197706 **BzS showed obvious in vitro hERα agonistic activities; BzS in particular exhibited a higher estrogenic activity compared to bisphenol A (BPA).** Registry of Toxic Effects of Chemical Substances (RTECS) https://www.cdc.gov/niosh-rtecs/VO1AB3F0.html	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/benzyl_salicylate Xi – Irritant H317 (95.53%): May cause an allergic skin reaction H319 (72.34%): Causes serious eye irritation Skin sensitisation (Category 1), H317 Eye irritation (Category 2A), H319 H371 - May cause damage to organs Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Hypersensitivity or excessive use may cause skin to blister, leading to an increase in pigmentation (Sulzberger & Wolf, 1942). Benzyl salicylate was reported to cause severe pruritus in six of 15 patients who applied it in a trioxsalen lotion (Kahn, 1971). Food and Cosmetics Toxicology. Vol. 11, Pg. 1029, 1973. Food Chem Toxicol. 2007;45 Suppl 1:S362-80 Dermal Systemic Exposure in Cosmetic Products: 0.40 mg/kg/day (IFRA, 2002) Pigmented contact dermatitis secondary to benzyl salicylate. Acta Derm Venereol. 2013 Sep 4;93(5):590
Boswellia Carterii Oil Frankincense Olibanum, Oil (Boswellia Spp.) 8016-36-2	FDA PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances	Not Listed	No PubChem listing R 20/21/22 - Harmful by inhalation, in contact with skin and if swallowed. R 36/37/38 - Irritating to eyes, respiratory system, and skin. R 42/43 - May cause sensitization by inhalation and skin contact.

Fragrance Chemical	21 CFR	IID	Other
	Sec. 172.510 Natural flavoring substances and natural substances used in conjunction with flavors.		http://www.thegoodscentscompany.com/data/es1004051.html
Bulnesia sarmienti. ext. bulnesia sarmienti extract bulnesia sarmienti extract acetate bulnesia sarmienti oil **Guaiac Wood Oil** 8016-23-7 89958-10-1	FDA PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.510 Natural flavoring substances and natural substances used in conjunction with flavors. Guaiac wood oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) included guaiac wood in the list of currently used flavoring substances temporarily admitted for use with a possible limitation on the active principle in the final product.	Not Listed	No PubChem listing Xi – Irritant R 38 - Irritating to skin. Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion. it was moderately irritating (Moreno, 1973). Found in the tree Bulnesia sarmienti Lor. (Fam. Zygophyllaceae). Cosmetic Uses: masking agents, skin conditioning Skin irritation (Category 2), H315 Food and Cosmetics Toxicology. Vol. 12, Pg. 905, 1974.
Butanoic acid, ethyl ester Ethyl Butyrate 105-54-4	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.60 - Synthetic flavoring substances and adjuvants. 172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.60 - Synthetic flavoring substances and adjuvants. Ethyl butyrate is found in appleand in many fruits e. g. apricot, banana, plum, tangerine etc. Ethyl butyrate was granted GRAS status by FEMA (1965) and is approved as GRAS by the FDA for food use. The Council of Europe (1970) listed ethyl butyrate, giving an ADI of 1 mg/kg. The Food Chemicals	Present in 2 drug products for oral administration at 1mg / 10 mL	https://pubchem.ncbi.nlm.nih.gov/compound/ethyl_butyrate#section=InChI-Key Xi – Irritant R 36/37/38 - Irritating to eyes, respiratory system, and skin Skin irritation (Category 2), H315 Eye irritation (Category 2A), H319 Specific target organ toxicity - single exposure (Category 3), Respiratory system, H335 Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 2, Pg. 327, 1964. Industrial Medicine and Surgery. Vol. 41, Pg. 31, 1972. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/204.pdf

Fragrance Chemical	21 CFR	IID	Other
	Codex (1972) has a monograph on ethyl butyrate. The Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for ethyl butyrate giving an unconditional ADI of 0-15 mg/kg, and Browning (1965) has also published a monograph on ethyl butyrate.		Ethyl butyrate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972).
Butanoic acid, pentyl ester Amyl Butyrate Pentyl butyrate 540-18-1	FDA PART 172 – FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. Pentyl butanoate is found in banana, apple and apricot fruits.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/10890#section=Top Xi – Irritant R 36/37/38 - Irritating to eyes, respiratory system, and skin. Food and Cosmetics Toxicology. Vol. 2, Pg. 327, 1964. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/709.pdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2013.3169/epdf Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
Camphor 1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one 76-22-2	310: NEW DRUGS **§ 310.502** - Certain drugs accorded new drug status through rulemaking procedures. **§ 310.531** - Drug products containing active ingredients offered over-the-counter (OTC) for the treatment of boils. **§ 310.545** - Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses. 330: OVER-THE-COUNTER (OTC) HUMAN DRUGS WHICH ARE GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED **§ 330.12** - Status of over-the-counter (OTC) drugs previously reviewed under the Drug Efficacy Study (DESI). 341: COLD, COUGH, ALLERGY, BRONCHODILATOR, AND	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/2537 Camphor oil white applied full strength to intact or abraded rabbit skin was mildly irritating (Hart, 1971). Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Camphor is rapidly absorbed from the mucous membranes and the gastrointestinal tract. ... It is also absorbed through inhalation, through dermal application, and by nasal instillation. Ford MD, Delaney KA, Ling LJ, Erickson T: Clinical Toxicology. W.B. Saunders Company., Philadelphia, PA. 2001, p. 339 H312 (10.82%): Harmful in contact with skin [Warning Acute toxicity, dermal] H315 (16.04%): Causes skin irritation [Warning Skin corrosion/irritation]

Fragrance Chemical	21 CFR	IID	Other
	ANTIASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE § 341.14 - Antitussive active ingredients. § 341.40 - Permitted combinations of active ingredients. § 341.74 - Labeling of antitussive drug products. § 341.85 - Labeling of permitted combinations of active ingredients. 346: ANORECTAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE § 346.16 - Analgesic, anesthetic, and antipruritic active ingredients. 216: HUMAN DRUG COMPOUNDING § 216.24 - Drug products withdrawn or removed from the market for reasons of safety or effectiveness. 172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.510 - Natural flavoring substances and natural substances used in conjunction with flavors. § 172.515 - Synthetic flavoring substances and adjuvants. Camphor Oil is the oil extracted from the wood of the Camphor tree Cinnamomum Camphora. Camphor oil has anti-inflammatory and analgesic properties and is used for its aromatic properties, as an insect repellant, in embalming fluids, and in various topical skin preparations. Camphor oil white was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) included camphor oil (Cinnamomum camphora) in the list of temporarily		H319 (16.04%): Causes serious eye irritation R 36/37/38 - Irritating to eyes, respiratory system, and skin. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/729.pdf Cosmetic Uses: denaturants film formers plasticisers Restricted from fragrance use in Canada

Fragrance Chemical	21 CFR	IID	Other
	admissible flavoring substances (provided no safrole is present in the final product) Registry of Toxic Effects of Chemical Substances (RTECS) https://www.cdc.gov/niosh-rtecs/EX12B128.html		
Caproic Acid Hexanoic acid 142-62-1	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. 173: SECONDARY DIRECT FOOD ADDITIVES PERMITTED IN FOOD FOR HUMAN CONSUMPTION § 173.315 - Chemicals used in washing or to assist in the peeling of fruits and vegetables. Caproic acid is a colourless oily liquid that smells like cheese. Caproic Acid is a saturated medium-chain fatty acid with a 6-carbon backbone. Caproic acid is found naturally in various plant and animal fats and oils. It is safe for human dietary consumption up to levels of 1g/kg Hexanoic acid occurs in milk fats (about 2%), in coconut oil (<1%), and in various palm and other oils Registry of Toxic Effects of Chemical Substances (RTECS): https://www.cdc.gov/niosh-rtecs/MO501BD0.html	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/8892#section=Top C - Corrosive. H311 (23.6%): Toxic in contact with skin [Danger Acute toxicity, dermal] H314 (100%): Causes severe skin burns and eye damage [Danger Skin corrosion/irritation] H318 (69.79%): Causes serious eye damage [Danger Serious eye damage/eye irritation] Harmful if swallowed, inhaled, or absorbed through skin. Material is **extremely destructive to tissue of mucous membranes** and upper respiratory tract, eyes and skin (PubChem). Severe eye irritation in rabbit at 750 mcg. Mild irritation of rabbit skin on 10 mg dose. LD50 on rabbit skin 630 microLiters/kg The substance can be absorbed into the body by inhalation of its aerosol and through the skin. /LABORATORY ANIMALS: **Developmental or Reproductive Toxicity**/ As with other saturated carboxylic acids, caproic acid caused **microencephaly and other abnormalities in frog embryos**. The degree of potency in the series of acids increased with hydrophobicity. Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons. New York, N.Y. (2001).., p. 5:718 **Cosmetic Uses:** **cleansing agents** **emulsifying agents** **masking agents** **perfuming agents** **surfactants**

Fragrance Chemical	21 CFR	IID	Other
			Acta Pharmacologica et Toxicologica. Vol. 18, Pg. 141, 1961. Journal of Pharmacy and Pharmacology. Vol. 21. Pg. 85. 1969. AMA Archives of Industrial Hygiene and Occupational Medicine. Vol. 10, Pg. 61, 1954. Journal of Industrial Hygiene and Toxicology. Vol. 26, Pg. 269, 1944. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/927.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/976.pdf
Caprylyl Alcohol? Could not locate. Could be Caprylyl Glycol or Caprylic Alcohol	Could Not Locate		
Carum Carvi (Caraway) Fruit Oil caraway seed oil 8000-42-8	FDA PART 182 -- SUBSTANCES GENERALLY RECOGNIZED AS SAFE Subpart A--General Provisions Sec. 182.20 Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). The main constituent of caraway oil is **carvone** (see above). Caraway oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included caraway oil (*Carum carvi*) in the list of substances, spices and seasonings whose use is deemed admissible, with a possible limitation of the active principle in the final product. Both the Food Chemicals Codex (1972) and the National Formulary (1970) have monographs on caraway oil.	Not Listed (refer to carvone)	https://pubchem.ncbi.nlm.nih.gov/compound/6850759 Xi – Irritant R 36/37/38 - Irritating to eyes, respiratory system, and skin. R 43 - May cause sensitisation by skin contact. Acute toxicity, dermal (Category 4), H312 Cosmetic Uses: masking agents perfuming agents Food and Cosmetics Toxicology. Vol. 11, Pg. 1051, 1973. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2014.3806/epdf The acute dermal LD 50 in the rabbit was reported to be 1.78 ml/kg (1.46-2.18 ml/kg) (Shelanski & Moldovan, 1972). Caraway oil applied full strength to intact or abraded rabbit skin was irritating (Shelanski & Moldovan, 1972).
Castoreum	FDA PART 182 -- SUBSTANCES GENERALLY RECOGNIZED AS SAFE Subpart A--General Provisions	Not Listed	No PubChem found. Int J Toxicol. 2007 Jan-Feb;26(1):51-5

Fragrance Chemical	21 CFR	IID	Other
Castoreum. Liquid (Castor SPP.) 8023-83-4	Sec. 182.50 Certain other spices. seasonings. essential oils. oleoresins. and natural extracts. Castoreum was granted GRAS status by FEM A (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included castoreum in the list of flavouring substances whose use is temporarily admitted. with a possible limitation on the active principle in the final product.		Safety assessment of castoreum extract as a food ingredient. Acute toxicity studies in animals indicate that castoreum extract is nontoxic by both oral and dermal routes of administration and is not irritating or phototoxic to skin. Skin sensitization has not been observed in human subject tests. Found as the secretion obtained from the oil glands of the beaver Castor fiber L. (Castoridae).
Cedrol (1S.2R.5S.7R.8R)-2.6.6.8-tetramethyltricyclo[5.3.1.01.5]undecan-8-ol Cedarwood oil alcohols. 77-53-2	Could not locate in CFR or an IFRA Standard Found in the wood of several conifers. particularly cypresses and cedars. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/978.pdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2010.1336/epdf	Not Listed Cedrol. beta-cedrene. and thujopsene are bioactive sesquiterpenes found in cedar essential oil and exert antiseptic. anti-inflammatory. antispasmodic. tonic. astringent. diuretic. sedative. insecticidal. and antifungal activities. These compounds are used globally in traditional medicine and cosmetics.	https://pubchem.ncbi.nlm.nih.gov/compound/65575 Xi – Irritant R 36/37/38 - Irritating to eyes. respiratory system. and skin. Cosmetic Uses: emollients masking agents skin conditioning Cedrol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno. 1973). A maximization test (Kligman. 1966: Kligman & Epstein. 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced sensitization reactions in two of the 25 test subjects (Kligman. 1973a; see Preface Note no. 1). Retested by the same maximization test on 25 volunteers. a concentration of 8% in petrolatum produced no sensitization reactions (Kligman. 1973b). Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 13. Pg. 745. 1975.
Cedrus Atlantica (Cedarwood) Bark Oil Cedarwood Oil Atlas	Not Located in CFR or an IFRA Standard Cedarwood oil atlas is not included in the listings of the FDA. FEMA (1965) or the	Not Listed	No PubChem Found Xi – Irritant R 36/37/38 - Irritating to eyes. respiratory system. and skin.

Fragrance Chemical	21 CFR	IID	Other
8023-85-6	Council of Europe or in the Food Chemicals Codex. The chief constituents of cedarwood oil atlas are a- and y-atlantone (Guenther, 1952).		Sensitization Undiluted cedarwood oil atlas applied to the backs of hairless mice and swine was not irritating (Urbach & Forbes, 1974) but applied to intact or abraded rabbit skin for 24 hr under occlusion it was slightly irritating (Moreno, 1974). http://www.thegoodscentscompany.com/search3.php?qName=cedarwood&submit.x=0&submit.y=0
Celery seed (Apium graveolens L.) Celery Seed Oil 8015-90-5 156465-88-2	FDA PART 182 -- SUBSTANCES GENERALLY RECOGNIZED AS SAFE Subpart A--General Provisions Sec. 182.20 Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). Celery seed oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included celery seed oil in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The Food Chemicals Codex (1972) has a monograph on celery seed oil.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/177972#section=Top Food and Cosmetics Toxicology, Vol. 12, Pg. 849, 1974. Xi – Irritant
Chamomilla Recutita (Matricaria) Flower Oil Apigenin 84082-60-0	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.10 - Spices and other natural seasonings and flavorings. § 582.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). 310: NEW DRUGS § 310.545 - Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses. 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.10 - Spices and other natural seasonings and flavorings.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/5280443#section=Top Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was moderately irritating (Moreno, 1973). Cosmetic ingredient for skin conditioning. Despite widescale use, chamomile has not been convincingly linked to instances of clinically apparent liver injury https://livertox.nlm.nih.gov/Chamomile.htm

Fragrance Chemical	21 CFR	IID	Other
	§ 182.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). Chamomile oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included chamomile oil {Matricaria chamomilla) in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The Food Chemicals Codex has a monograph on chamomile oil.		
Cinnamal cinnamaldehyde 3-phenyl-2-propenal 104-55-2 Cinnamaldehyde is the aldehyde that gives cinnamon its flavor and odor. Cinnamaldehyde occurs naturally in the bark of cinnamon trees and other species of the genus Cinnamomum like camphor and cassia. These trees are the natural source of cinnamon, and the essential oil of cinnamon bark is about 90% cinnamaldehyde. Cinnamaldehyde is also used as a fungicide. Concentrated cinnamaldehyde is a skin irritant, and the chemical is toxic in large doses, but no agencies suspect the compound is a carcinogen or poses a long-term health hazard.	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.60 - Synthetic flavoring substances and adjuvants. 172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.60 - Synthetic flavoring substances and adjuvants. IFRA fragrance material specification: The concentration of Cinnamic aldehyde in the finished cosmetic product should not exceed 0.1%.	Not Listed **Cinnamaldehyde is a Standardized Chemical Allergen.** The physiologic effect of cinnamaldehyde is by means of Increased Histamine Release, and Cell-mediated Immunity. The chemical classification of cinnamaldehyde is Allergens.	https://pubchem.ncbi.nlm.nih.gov/compound/637511 H315 (100%): Causes skin irritation H317 (100%): May cause an allergic skin reaction H319 (100%): Causes serious eye irritation Skin irritation (Category 2), H315 Skin sensitization (Category 1), H317 Eye irritation (Category 2A), H319 Skin Sensitivity testing Johansen JD et al: Contact Dermatitis 34 (3): 165-71 (1996). 1% of 21,325 patients were sensitive to skin patch test Schnuch A et al; Contact Dermatitis 57 (1): 1-10 (2007) LD50 Rabbit skin 0.59 mg/kg Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons, New York, N.Y. (2001)., p. V5 1044 Food and Cosmetics Toxicology, Vol. 2, Pg. 327, 1964. Cinnamon oil contains local mucous membrane irritants such as cinnamaldehyde. Prolonged skin contact (over 48 hours) from a cinnamon oil spill produced superficial partial-thickness burns. Ellenhorn, M.J. and D.G. Barceloux, Medical Toxicology - Diagnosis and Treatment of Human Poisoning, New York, NY: Elsevier Science Publishing Co., Inc. 1988., p. 1299

Fragrance Chemical	21 CFR	IID	Other
			Reproductive Tox Studies Adams TB et al: Food and Chem Toxicol 42: 157-185 (2004) Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
Cinnamyl Alcohol 3-phenyl-2-propen-1-ol 104-54-1	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. 189: SUBSTANCES PROHIBITED FROM USE IN HUMAN FOOD § 189.113 - Cinnamyl anthranilate. (An ester of CA is prohibited) Cinnamic alcohol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) listed cinnamic alcohol giving an ADI of 1.25 mg/kg. The Food Chemicals Codex has a monograph on cinnamic alcohol. Found as an ester or in the free state in several natural products (cinnamon leaves, hyacinth, Aristolochia clematis, and Xanthorrhoea hastilis) and also in the essence of daffodil flowers (Fenarolfs Handbook of Flavor Ingredients, 1971). European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/880.pdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1032/epdf	Not Listed Cinnamyl alcohol is approved by the FDA for use within allergenic epicutaneous patch tests which are indicated for use as an aid in the diagnosis of allergic contact dermatitis (ACD) in persons 6 years of age and older. Standardized Chemical Allergen	https://pubchem.ncbi.nlm.nih.gov/compound/5315892 Xi - Irritant R 36/38 - Irritating to skin and eyes. R 43 - May cause sensitisation by skin contact. Skin irritation (Category 2), H315 Skin sensitisation (Category 1), H317 Eye irritation (Category 2A), H319 H317 - May cause an allergic skin reaction Cinnamyl alcohol is 66% absorbed through the skin and shown to be rapidly absorbed from the gut Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 12. Pg. 855. 1974. Cinnamic alcohol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Greif, 1967). Positive reactions to 5% cinnamic alcohol in vaseline were reported in 26 out of 144 patients who were already sensitized to Peru balsam (Hjorth, 1961). Skin Patch Test Sensitization LARSEN WG, ARCH DERMATOL 113(5) 623 (1977) Reactions in selected patients to 22 fragrance materials. Contact Dermatitis. 1984 Jul;11(1):1-10

Fragrance Chemical	21 CFR	IID	Other
			Fragrance usage is IFRA RESTRICTED. http://www.ifraorg.org/en-us/standards-library/open/23615#.W2-B9ehKiUm
Citral 3,7-dimethyl-2,6-octadienal **Geranial** Lemonal 5392-40-5	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.60 - Synthetic flavoring substances and adjuvants. 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.60 - Synthetic flavoring substances and adjuvants. Geranial is found in apricot. Geranial occurs in lemon grass oil (Cymbopogon citratus), lemon, orange and many other essential oils Evaluations of the Joint FAO/WHO Expert Committee on Food Additives – JECFA. Use of citral as a flavouring agent is subsumed in the 1979 group ADI of 0-0.5 mg/kg bw for citral, geranyl acetate, citronellol, linalool, and linallyl acetate, expressed as citral, which was maintained at the sixty-first meeting. http://apps.who.int/iris/bitstream/handle/10665/42849/WHO_TRS_922.pdf;jsessionid=F2240BD35551A5B5BD9B60755250D758?sequence=1 Registry of Toxic Effects of Chemical Substances (RTECS) https://www.cdc.gov/niosh-rtecs/RG4D7038.html European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1024/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1025/epdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/638011 Absorbed through skin Diliberto JJ et al; Drug Metab Dispos 16 (5): 721-7 (1988) H315 (100%): Causes skin irritation H317 (23.56%): May cause an allergic skin reaction H319 (66.67%): Causes serious eye irritation Xi - Irritant R 38 - Irritating to skin. R 43 - May cause sensitisation by skin contact. Skin irritation (Category 2), H315 Skin sensitisation (Category 1), H317 Skin Irritant Rothenborg HW et al; Contact Dermatitis 3 (1): 37 (1977) Severe Skin Irritant, 16 mg/48H on males Cosmetics and Toiletries, 94(8),41,1979 Mild skin irritant, 40 mg/24H on human Food and Cosmetics Toxicology 17,259,1979 Food and Cosmetics Toxicology, Vol. 2, Pg. 327, 1964. Food and Chemical Toxicology, Vol. 25, Pg. 505, 1987. Food Chem Toxicol. 2014 Jun;68:71-7 Evaluation of toxicity of essential oils palmarosa, citronella, lemongrass and vetiver in human lymphocytes Citral induced cytotoxicity and genotoxicity at higher concentrations Selective oocyte degeneration and impaired fertility in rats treated with the aliphatic monoterpene, Citral. J Reprod Fertil. 1979 Mar;55(2):347-52 "Mature female rats treated with Citral (3-7-dimethyl-2,6-octadienal) either topically for 60 or 100 days or by 6 i.p. injections (at 4-5 day day intervals) showed a marked decrease in the number of normal follicles per section, because oocytes tended to degenerate although the follicular cells remained normal. The

Fragrance Chemical	21 CFR	IID	Other
			reproductive performance after Citral treatment was impaired: there was a reduction in implantation number and litter size and an increased post-implantation fetal wastage. None of the young survived after 100 days of topical Citral treatment. It is suggested that Citral directly affects the oocytes." Valid genotoxicity result in chinese hamster ovary cells at 0.289–40.2 ug/ml NTP. 2003e. NTP technical report on the toxicology and carcinogenesis studies of citral (microencapsulated) (CAS No. 5392-40-5) in F344/N rats and B6C3F1 mice (feed studies). (NTP TR 505; NIH Publication No. 01-4439). US Department of Health and Human Services, Public Health Service, National Institutes of Health, USA. Contact allergy to air-exposed geraniol: clinical observations and report of 14 cases Contact Dermatitis. 2012 Jul:67(1):20-7 Citral a fragrance allergen and irritant. Contact Dermatitis. 2003 Jul:49(1):32-6. Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Fragrance usage is IFRA RESTRICTED http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl
Citrus Aurantifolia (Lime) Oil citrus aurantiifolia swingle oil 8008-26-2 90063-52-8	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates).	Not Listed	PubChem not found IFRA Use Restriction Standard due to phototoxicity Evaluation of phototoxic properties of fragrances. Acta Derm Venereol. 2007;87(4):312-6. Food and Cosmetics Toxicology. Vol. 12, Pg. 729, 1974. Lime oil applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Hart 1971).

Fragrance Chemical	21 CFR	IID	Other
	The main constituent of lime oil distilled is d-limonene (Gildemeister & Hoffman. 1959; Guenther. 1949). Lime oil was granted GRAS status by FEMA (1965) and is approved as GRAS by the FDA for food use. The Council of Europe (1970) included lime oil in the list of substances, spices and seasonings whose use is deemed admissible, with a possible limitation of the active principle in the final product. The Food Chemicals Codex has a monograph on lime oil distilled.		
Citrus Aurantium Bergamia (Bergamot) Fruit Oil 89957-91-5 8007-75-8	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). Bergamot oil was granted GRAS status by FEM A (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included bergamot oil (Citrus bergamia) in the list of substances, spices and seasonings whose use is deemed admissible, with a possible limitation of the active principle in the final product. The Food Chemicals Codex has a monograph on bergamot oil.	Not Listed	No PubChem found Xi – Irritant R 36/37/38 - Irritating to eyes, respiratory system, and skin. R 43 - May cause sensitisation by skin contact. Severe phototoxic effects have been reported for bergamot oil expressed, using simulated sunlight on hairless mice, pigs and man (Urbach & Forbes, 1972). Severe phototoxic reactions to bergamot oil, expressed, were induced in man using natural sunlight (Wild, 1971). No There are several articles in the dermatological literature relating bergamot oil and berloque dermatitis. The Photodermatitis has been attributed to the content of 5-methoxypsoralen in the expressed oil. This may be as high as 0-39 %. IFRA Use Restriction Due to Phototoxicity http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl limits in the finished product for - "leave on the skin contact": 0.4000 % Restriction. Good Scents Notes: This oil should not be used anywhere on the body because of its phototoxic effects. from citrus bergamia; used in perfume; some of its constituents contribute to its photosensitization. tsca

Fragrance Chemical	21 CFR	IID	Other
			definition 2008: extractives and their physically modified derivatives. citrus bergamia. citrus. Toxic profile of bergamot essential oil on survival and proliferation of SH-SY5Y neuroblastoma cells. Food Chem Toxicol. 2011 Nov;49(11):2780-92 https://www.ncbi.nlm.nih.gov/pubmed/21878361 Bergamot essential oil triggered concentration-dependent mitochondrial dysfunction, cytoskeletal reorganization, cell shrinkage, DNA fragmentation and both caspase-dependent and independent cell death. Analysis of cleavage products of poly-(ADP-ribose) polymerase (PARP) revealed caspase-3 activation, but also activation of additional protease families. As result of increased proteolytic activity, Akt protein levels decreased in BEO-treated cells. Our data show that BEO can be lethal for dividing cells by activating multiple pathways. Phototoxicity of bergamot oil assessed by in vitro techniques in combination with human patch tests. Toxicol In Vitro. 2007 Oct;21(7):1298-303 https://www.ncbi.nlm.nih.gov/pubmed/17669618 Evaluation of phototoxic properties of fragrances. Acta Derm Venereol. 2007;87(4):312-6. https://www.ncbi.nlm.nih.gov/pubmed/17598033 Genotoxicity of bergapten and bergamot oil in Saccharomyces cerevisiae. J Photochem Photobiol B. 1990 Nov;7(2-4):209-29. https://www.ncbi.nlm.nih.gov/pubmed/2128325 Contact dermatitis caused by bergamot oil. Derm Beruf Umwelt. 1984;32(3):95-7. https://www.ncbi.nlm.nih.gov/pubmed/6236066
Citrus Aurantium Dulcis (Orange) Peel Oil Orange Peel, Sweet, Oil (Citrus Sinensis (L.) Osbeck The main component is Limonene (see above)	FDA PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart C--Coatings, Films and Related Substances Sec. 172.230 Microcapsules for flavoring substances.	Orange Flavor, Orange Extract, and Orange Oil in multiple approved drug products for Oral Admin.	PubChem not found Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion it was moderately irritating (Moreno, 1973). Food and Cosmetics Toxicology, Vol. 12, Pg. 733, 1974. IFRA Use Restriction Due to Phototoxicity

Fragrance Chemical	21 CFR	IID	Other
68916-04-1	FDA PART 182 -- SUBSTANCES GENERALLY RECOGNIZED AS SAFE Subpart A--General Provisions Sec. 182.20 Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). Orange oil was granted GRAS status by FEMA (1965) and is approved by the FDA as GRAS for food use. The Council of Europe (1970) included orange oil in the list of substances, spices and seasonings whose use is deemed admissible, with a possible limitation of the active principle in the final product. The Food Chemicals Codex (1972) and the United States Pharmacopeia (1965) both have monographs on orange oil.		http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2013.EN-440/pdf http://www.thegoodscentscompany.com/data/es1719821.html
Citrus Medica Limonum (Lemon) Peel Oil Lemon oil 8008-56-8 The main constituent of lemon oil is d-limonene (See Above) (Gildemeister & Hoffman. 1959; Guenther. 1949).	FDA PART 146 -- CANNED FRUIT JUICES Subpart B--Requirements for Specific Standardized Canned Fruit Juices and Beverages Sec. 146.114 Lemon juice. FDA PART 146 -- CANNED FRUIT JUICES Subpart B--Requirements for Specific Standardized Canned Fruit Juices and Beverages Sec. 146.120 Frozen concentrate for lemonade. FDA PART 161 -- FISH AND SHELLFISH Subpart B--Requirements for Specific Standardized Fish and Shellfish Sec. 161.190 Canned tuna. FDA PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart C--Coatings, Films and Related Substances	Approved in 4 drug products for oral administration and one drug product for topical administration (0.05% w/w). Lemon oil was granted GRAS status by FEM A (1965) and is approved by the FDA as GRAS for food use. The Council of Europe (1970) included lemon oil in the list of substances, spices and seasonings whose use is deemed admissible, with a possible limitation of the active principle in the final product. The Food Chemicals Codex (1972) and the United States Pharmacopeia (1965) have monographs on lemon oil.	PubChem Not Found Lemon oil applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Hart, 1971). Three samples of lemon oil (RIFM nos 72-32, 72-61 and 72-241) applied undiluted to the backs of hairless mice were mildly irritating (Urbach & Forbes, 1972), but three other samples of lemon oil (RIFM nos 72- 249, 72-230 and 72-251) similarly applied undiluted to the backs of hairless mice were not irritating (Urbach & Forbes, 1972). Distinct phototoxic effects were reported by Urbach & Forbes (1972) for five samples of lemon oil—RIFM nos 72-61, 72-249, 72-250 (Italian), 72-241 (Greek) and 72-251 (Ivory Coast). Low-level phototoxic effects were reported for lemon oil (California; RIFM no. 72-32) (Urbach & Forbes, 1972). Cosmetic Uses: masking agents perfuming agents skin conditioning Pharmazie, Vol. 14, Pg. 435, 1959. Food and Cosmetics Toxicology, Vol. 12, Pg. 725, 1974. IFRA Use Restriction Due to Phototoxicity

Fragrance Chemical	21 CFR	IID	Other
	Sec. 172.230 Microcapsules for flavoring substances. FDA PART 173 -- SECONDARY DIRECT FOOD ADDITIVES PERMITTED IN FOOD FOR HUMAN CONSUMPTION Subpart C--Solvents, Lubricants, Release Agents and Related Substances Sec. 173.240 Isopropyl alcohol. FDA PART 182 -- SUBSTANCES GENERALLY RECOGNIZED AS SAFE Subpart A--General Provisions Sec. 182.20 Essential oils, oleoresins (solvent-free), and natural extractives (including distillates).		http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl A study of the phototoxicity of lemon oil. Arch Dermatol Res. 1985;278(1):31-6 Do not use on skin.tsca definition 2008: extractives and their physically modified derivatives, citrus limonum, citrus.
Citrus Nobilis (Mandarin Orange) Peel Oil 84929-38-4 8008-31-9	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates).	Approved in 1 drug product for oral administration at 0.01%.	PubChem Not Found Food and Chemical Toxicology, Vol. 30, Pg. 69S, 1992 Cosmetic Uses: masking agents perfuming agents skin conditioning
Commiphora Myrrha Resin Myrrh Oil Oil of Heerabol-Myrrh 84929-26-0 9000-45-7	FDA PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.510 Natural flavoring substances and natural substances used in conjunction with flavors. Myrrh oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1974) included myrrh oil in the list of substances, spices and seasonings deemed admissible for use, with a	Not Listed	PubChem Not Found Xi - Irritant R 36/38 - Irritating to skin and eyes. Cosmetic Uses: masking agents http://www.thegoodscentscompany.com/data/rs1008771.html

Fragrance Chemical	21 CFR	IID	Other
	possible limitation of the active principle in the final product. The Food Chemicals Codex (1972) has a monograph on myrrh oil.		
Copper Chlorophyll chlorophylls, copper complexes 15611-43-5 65963-40-8	357: MISCELLANEOUS INTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE § 357.810 - Active ingredients for deodorant drug products for internal use. § 357.850 - Labeling of deodorant drug products for internal use. 73: LISTING OF **COLOR ADDITIVES** EXEMPT FROM CERTIFICATION § 73.125 - Sodium copper chlorophyllin. § 73.1125 - Potassium sodium copper chloropyhllin (chlorophyllin-copper complex). § 73.2125 - Potassium sodium copper chlorophyllin (chlorophyllin-copper complex). § 73.3110 - Chlorophyllin-copper complex, oil soluble. Joint FAO/WHO Expert Committee on Food Additives set an ADI of 0-15 mg/kg. No IFRA Standard	Not Listed No longer allowed for drug product use, except in dentrifices. **No longer allowed for cosmetic use except in dentrifices at less than 0.1% May be used only in combination with the substances listed in 21 CFR 73.2125(b)(2) - 73.2125**	https://pubchem.ncbi.nlm.nih.gov/compound/22833293#section=Top Category: coloring agents blue green to dark green waxy solid European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2015.4151/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2016.4391/epdf
Coriandrum Sativum (Coriander) Fruit Oil Coriander Seed Oil 8008-52-4 The main constituent of coriander oil is linalool (Guenther, 1950). See above	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.10 - Spices and other natural seasonings and flavorings. § 582.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.10 - Spices and other natural seasonings and flavorings. § 182.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates).	Approved in 2 drug products for oral administration at up to 3%.	Pubchem Not Found Coriander oil applied full strength to intact or abraded rabbit skin was irritating (Hart, 1971). Xi - Irritant R 36/37/38 - Irritating to eyes, respiratory system, and skin. R 43 - May cause sensitisation by skin contact. Cosmetic Uses: masking agents perfuming agents IFRA Use Restriction due to sensitization http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMymqUl

Fragrance Chemical	21 CFR	IID	Other
	Coriander oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included coriander oil (Coriandrum sativum) in the list of substances, spices and seasonings whose use is deemed admissible, with a possible limitation of the active principle in the final product. The Food Chemicals Codex (1972) and the United States Pharmacopeia (1965) have monographs on coriander oil.		Food and Cosmetics Toxicology. Vol. 11. Pg. 1077. 1973. Tokishikoroji Foramu. Toxicology Forum. Vol. 8. Pg. 91. 1985. Food and Chemical Toxicology 47 (2009) 22–34 The symptoms of allergy to coriander may vary from itching and stinging of the lips and mouth to anaphylactic shock. Some investigators have reported positive skin prick tests and specific IgE production to coriander European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2013.EN-440/pdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2013.3422/epdf
Coumarin 1-benzopyran-2-one 91-64-5 Found in many plants and essential oils such as cassia, melilot, orchid, lavender and balsam of Peru (Späth, 1937; Gildemeister & Hoffman, 1966).	**189: SUBSTANCES PROHIBITED FROM USE IN HUMAN FOOD** **§ 189.130 - Coumarin.** The use of coumarin as a food additive was banned by the FDA in 1954 based on reports of **hepatotoxicity** in rats. It has clinical value as the precursor for several anticoagulants, notably warfarin. Coumarin is also used clinically as an antineoplastic and for the treatment of lymphedema and venous insufficiency. **Recent evidence indicates coumarin causes liver tumors in rats and mice and Clara cell toxicity and lung tumors in mice.** No epidemiological data relevant to the carcinogenicity of coumarin were available. There is limited evidence in experimental animals for the carcinogenicity of coumarin. Overall evaluation: Coumarin is not classifiable as to its carcinogenicity to humans (Group 3). IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans.	Not Listed.	https://pubchem.ncbi.nlm.nih.gov/compound/323 H317 (90.48%): May cause an allergic skin reaction [Warning Sensitization, Skin] H373 (12.1%): Causes damage to organs through prolonged or repeated exposure IFRA Use Restriction Due to Sensitization http://www.ifraorg.org/en-us/standards-library/open/23615#.W3HMfOhKiUm Category 5 Restriction Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Yourick JJ, et al; J Appl Toxicol 17(3): p 153-8 (1997) Coumarin rapidly penetrated both rat and human skin with > 75% and > 95%, respectively, of the absorbed dose found in the receptor fluid within 6 h. No evidence of coumarin metabolism was found in either skin or receptor fluid fractions. These studies indicate that coumarin absorption is significant in skin. Systemic coumarin absorption must be expected after dermal contact with coumarin-containing products. Additional skin adsorption studies:

Fragrance Chemical	21 CFR	IID	Other
	Geneva: World Health Organization. International Agency for Research on Cancer. 1972-PRESENT. (Multivolume work). Available at: http://monographs.iarc.fr/ENG/Classification/index.php V77 217 (2000) European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/104.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/793.pdf Registry of Toxic Effects of Chemical Substances (RTECS) https://www.cdc.gov/niosh-rtecs/GN401640.html		Senam A.J. Beckley-Kartey, et al: Toxicology and Applied Pharmacology 145 (1): 34-42 (1997) Registry of Toxic Effects of Chemical Substances (RTECS) https://www.cdc.gov/niosh-rtecs/GN401640.html Reproductive: Effects on embryo or fetus: Fetotoxicity (except death, e.g., stunted fetus) in rats following 3.6 g/kg oral dose ARZNAD (Arzneimittel-Forschung, Drug Research) 17.97.1967 Cytogenetic to CHO cells at dose of 100 - 1600 mg/L Environmental and Molecular Mutagenesis. 10(Suppl 10),1.1987 Food and Cosmetics Toxicology. Vol. 12, Pg. 385, 1974. Yakugaku Zasshi. Journal of Pharmacy. Vol. 83, Pg. 1124, 1963. LIVER: LIVER FUNCTION TESTS IMPAIRED Human Toxicology. Vol. 8, Pg. 501, 1989. Chronic toxicity (dermal route). A single application of 15% coumarin in acetone to mouse skin failed to produce epidermal hyperplasia within 3 days of dosage and no tumour-initiating activity was seen after either a single dose of 45 mg coumarin (15% in acetone) or a total dose of 150 mg coumarin (one dose of 10% in acetone followed by 12 weekly doses of 3-3% in acetone) to mouse skin followed in both cases by treatment with the tumour promoter, croton oil (Roe & Salaman, 1955). Percutaneous absorption. Rabbits dosed dermally or orally with coumarin showed a similar pattern in the urinary excretion of coumarin metabolites (Pekker & Schäfer, 1969). NTP Toxicology and Carcinogenesis Studies of Coumarin (CAS No. 91-64-5) in F344/N Rats and B6C3F1 Mice (Gavage Studies). Natl Toxicol Program Tech Rep Ser. 1993 Sep;422:1-340. Definitive Tox and Carcinogentic study: clear evidence of carcinogenticity in female mice. https://www.ncbi.nlm.nih.gov/pubmed/12616289
Cuminum Cyminum (Cumin) Seed Oil cuminum cyminum fruit	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates).	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/6850782 R 36/37/38 - Irritating to eyes, respiratory system, and skin. Food and Cosmetics Toxicology. Vol. 12, Pg. 869, 1974.

Fragrance Chemical	21 CFR	IID	Other
The main constituent of cumin oil is cuminaldehyde (Gildemeister & Hoffman, 1961; Guenther, 1950). 8014-13-9 84775-51-9	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). 101: FOOD LABELING § 101.22 - Foods: labeling of spices, flavorings, colorings and chemical preservatives. Cumin oil was granted GRAS status by FEM A (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included cumin oil in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The Food Chemicals Codex (1972) has a monograph on cumin oil.		IFRA Use Restriction due to Phototoxicity http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2013.EN-440/pdf Phototoxicity. Distinct phototoxic effects were reported for undiluted cumin oil, but none for its principal ingredient, cuminaldehyde (Urbach & Forbes, 1972). Percutaneous absorption. Cumin oil was rapidly absorbed through the skin of the mouse (Meyer & Meyer, 1959). Irritation. Cumin oil applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Shelanski, 1972).
Cyclamen Aldehyde 3-(p-cumenyl)-2-methylpropionaldehyde 103-95-7	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Cyclamen aldehyde was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) included cyclamen aldehyde in the list of admissible artificial flavouring substances, at a level of 1 ppm. The Food Chemicals Codex (1972) has a monograph on cyclamen aldehyde. European Food Safety Authority (EFSA) reference(s):	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/517827 Xi – Irritant H315 (99.92%): Causes skin irritation [Warning Skin corrosion/irritation] H317 (94.48%): May cause an allergic skin reaction [Warning Sensitization, Skin] H361 (14.19%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity] Results of an Oral Range Finding Reproductive Toxicity Study in Rats with Cyclamen Aldehyde Environmental Protection Agency, Washington, DC. Office of Toxic Substances. 2009 Report Number OTS-8EHQ-0609-17555A Stock Number OTS0603046

Fragrance Chemical	21 CFR	IID	Other
	http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/638.pdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2017.4672/epdf		Cosmetic Uses: masking agents Food and Cosmetics Toxicology. Vol. 2. Pg. 327. 1964. Dermal Tox Study National Technical Information Service, Vol. OTS0535055 IFRA Use Restriction due to Sensitizer http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl Irritation. Cyclamen aldehyde tested at 3% in petrolatum produced a mild irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1971). Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
Decanal Capraldehyde Aldehyde C-10 Decyl aldehyde 112-31-2 Decyl aldehyde is the most widely occurring of all the fatty aldehydes. Over 50 sources including citrus oils, citronella and lemongrass contain this aldehyde (Gildemeister & Hoffman, 1963).	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.60 - Synthetic flavoring substances and adjuvants. 172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.60 - Synthetic flavoring substances and adjuvants. Aldehyde C-10 was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1972) listed aldehyde C-10 (decanal), giving an ADI of 1 mg/kg. The Food Chemicals Codex (1972) has a monograph on aldehyde C-10.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/8175 H315 (25.17%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (93.63%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] Xi N - Irritant. Dangerous for the environment. R 38 - Irritating to skin. Severe irritation to rabbit skin at 14372 ug/24H AIHAAP American Industrial Hygiene Association Journal. (AIHA, 475 Wolf Ledges Pkwy., Akron, OH 44311) V.19-1958- Volume(issue)/page/year: 23,95,1962 skin-rabbit 500 mg/24hours mild FCTXAV 11,1079,1973 Cosmetic Uses: masking agents The acute dermal L D 50 for rabbits is given as 5-04 ml/kg (Smyth et al. 1962). Fragrance Chemicals of Concern Present on the IFRA List 2015:

Fragrance Chemical	21 CFR	IID	Other
	European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2013.3169/epdf		https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Decanal was cytotoxic to Hela cells with IC50 less than 20 ug/mL. Cytotoxicity was evaluated on Hela cells using the 3-(4,5-dimethyl-thiazol-2-yl)-2,5-diphenyl tetrazolium bromide assay. All test samples showed significant cytotoxicity on the cell lines with IC(50) values much less than 20 ug/mL. [Liu K et al; J Food Sci 77 (11): C1156-61 (2012)]
Dimethylhydroquinone para-dimethyl hydroquinone p-dimethoxybenzene 150-78-7	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. **Registry of Toxic Effects of Chemical Substances (RTECS)** https://www.cdc.gov/niosh-rtecs/CZ657890.html **Mild to moderate skin irritation in rabbit skin studies** **Eye Irritation** **Toxicology Review** **Human Toxicology 1996 577** **Mutation Research 2014 762 76** European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/417.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/639.pdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/9016 H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (92.86%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] Xi - Irritant R 36/38 - Irritating to skin and eyes. Coumarin replacer. Chronic neurotoxic effects include vision disturbances O'Donoghue, J.L. (ed.). Neurotoxicity of Industrial and Commercial Chemicals. Volume I. Boca Raton, FL: CRC Press, Inc., 1985., p. 129 Food and Cosmetics Toxicology. Vol. 16, Pg. 715, 1978. Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
Ethyl 3-methyl-3-phenyloxirane-2-carboxylate **Ethyl Methylphenylglycidate** Strawberry Glycidate 1 Aldehyde C-16	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.60 - Synthetic flavoring substances and adjuvants.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/12321596 H317 (77.27%): May cause an allergic skin reaction [Warning Sensitization, Skin] Xi N - Irritant, Dangerous for the environment. R 36 - Irritating to eyes.

Fragrance Chemical	21 CFR	IID	Other
77-83-8	182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.60 - Synthetic flavoring substances and adjuvants. Ethyl methylphenylglycidate was granted GRAS status by FEM A (1965) and is approved by the FDA for food use. **The Council of Europe (1970) listed ethyl methylphenylglycidate among the artificial flavoring substances not admissible at present including it in the group "Biological Data Indicate Definite Toxicity"**. The Food Chemicals Codex (1972) has a monograph on ethyl methylphenylglycidate and that published by the Joint FAO/WHO Expert Committee on Food Additives (1967) gives a temporary ADI of 0-0.6 mg/kg. The ADI was revised to 0.5 mg/kg in 1984. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/811.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/937.pdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2014.3708/epdf		Skin irritation (Category 2), H315 Eye irritation (Category 2A), H319 Chronic toxicity. In a feeding study in rats, a dietary level of 10,000 ppm given for 16 wk caused growth retardation, particularly in males, and marked testicular atrophy, while 2500 ppm fed to a similar group for 1 yr produced no effects (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967). In a 2-yr feeding study, male and female rats fed a diet containing 5000 ppm ethyl methylphenylglycidate exhibited paralysis of the hindquarters as well as demyelinating degenerative changes in the sciatic nerve (Bär & Griepentrog, 1967). No effect was observed with a dietary level of 1000 ppm, but a subsequent paper (Griepentrog, 1969) reported the finding of effects at all levels when groups of rats were fed diets containing 1000, 3500, 5000 or 6000 ppm ethyl methylphenylglycidate for 2 yr. In these four groups the histological changes of the sciatic nerve were found in 22, 70, 65 and 60% respectively, the effects being marked in 17, 20, 40 and 40% respectively. No histological changes were found in the other organs studied, namely the liver, kidney, spleen and heart. Study of artificial flavouring substances for mutagenicity in the Salmonella/microsome, Base and micronucleus tests. Food Chem Toxicol. 1983 Dec;21(6):707-19. ethyl 3-methyl-3-phenylglycidate appeared weakly mutagenic in Drosophila only Food and Cosmetics Toxicology, Vol. 2, Pg. 327, 1964. Food Cosmet Toxicol. 1978 Aug;16(4):331-6. Food Cosmet Toxicol. 1981 Dec;19(6):691-9. Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ EFSA Considerations ethyl methylphenylglycidate [FL-no: 16.015] ... there is substantial evidence of a genotoxic potential from the available in vitro and in vivo studies. Sister chromatid exchange in hamster ovary cells at doses of 16, 50, or 160 µg/mL

Fragrance Chemical	21 CFR	IID	Other
			Galloway SM, Armstrong MJ, Reuben C, Colman S, Brown B, Cannon C, Bloom AD, Nakamura F, Ahmed M, Duk S, Rimpo J, Margolin BH, Resnick MA, Anderson B and Zeiger E. 1987. Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. Environmental and Molecular Mutagenesis 10(Suppl. 10), 1-175.
Ethyl Benzoate benzoic acid, ethyl ester 93-89-0	FDA PART 172 – FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. Ethyl benzoate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) listed ethyl benzoate, giving an ADI of 5 mg/kg. The Food Chemicals Codex has a monograph on ethyl benzoate and Browning (1965) has published an extensive monograph on this ester.		https://pubchem.ncbi.nlm.nih.gov/compound/7165 Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Xi – Irritant R 36/38 - Irritating to skin and eyes. S 24/25 - Avoid contact with skin and eyes. H319 (72.29%): Causes serious eye irritation Tox Study in cat skin 10gm/kg (10000mg/kg) BEHAVIORAL: MUSCLE WEAKNESS GASTROINTESTINAL: CHANGES IN STRUCTURE OR FUNCTION OF SALIVARY GLANDS BEHAVIORAL: TREMOR Journal of Pharmacology and Experimental Therapeutics. Vol. 84, Pg. 358, 1945.
Ethyl heptanoate ethyl capronate ETHYL OENANTHATE cognac oil synthetic 106-30-9	FDA PART 172 – FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. Cognac oil was given GRAS status by FEMA and is approved by the FDA for food use (GRAS). The Food Chemicals Codex has a monograph on cognac oil, green.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/7797 Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Xi – Irritant R 36/38 - Irritating to skin and eyes. Food and Cosmetics Toxicology. Vol. 19, Pg. 247, 1981. Applied full strength to intact or abraded rabbit and guinea-pig skin for 24 hr under occlusion, it was slightly irritating (Moreno, 1974). Tested
Ethyl Vanillin 121-32-4	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.60 - Synthetic flavoring substances and adjuvants.	Approved in 7 drug products, all for oral administration, up 0.6 mg per dose.	https://pubchem.ncbi.nlm.nih.gov/compound/ethyl_vanillin H315 (14.69%): Causes skin irritation H319 (82.45%): Causes serious eye irritation

Fragrance Chemical	21 CFR	IID	Other
	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.60 - Synthetic flavoring substances and adjuvants. § 182.90 - Substances migrating to food from paper and paperboard products. 169: FOOD DRESSINGS AND FLAVORINGS § 169.181 - Vanilla-vanillin flavoring. Ethyl vanillin was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) listed ethyl vanillin, giving an ADI of 10 mg/kg. The Food Chemicals Codex (1972) and the National Formulary (1970) each has a monograph on ethyl vanillin and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for ethyl vanillin giving an unconditional ADI of 0-10 mg/kg.		Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ A human skin irritant. Lewis, R.J. Sax's Dangerous Properties of Industrial Materials. 9th ed. Volumes 1-3. New York, NY: Van Nostrand Reinhold, 1996., p. 1610 Highly irritating action on the eyes and mucous membranes of the respiratory tract. /Aldehydes/ Lewis, R.J. Sax's Dangerous Properties of Industrial Materials. 9th ed. Volumes 1-3. New York, NY: Van Nostrand Reinhold, 1996., p. 84 Ethyl vanillin tested at 2% in petrolatum produced a mild irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1970).
Eugenol 4-allyl-1-hydroxy-2-methoxybenzene 4-allyl guaiacol 97-53-0	872: DENTAL DEVICES § 872.3275 - Dental cement. 582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.60 - Synthetic flavoring substances and adjuvants. 310: NEW DRUGS § 310.545 - Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses. 172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants.	Approved in one drug product as an oral elixir. Quantity is unknown. There are a number of unapproved OTC products that advertise it for the use of toothache. Eugenol is also commonly used in combination with zinc oxide in dental procedures for the cementation of	https://pubchem.ncbi.nlm.nih.gov/compound/3314 H317 (99.88%): May cause an allergic skin reaction H319 (94.97%): Causes serious eye irritation R 42/43 - May cause sensitization by inhalation and skin contact. Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ **Eugenol is a Standardized Chemical Allergen**. The physiologic effect of eugenol is by means of Increased Histamine Release, and Cell-mediated Immunity. The chemical classification of eugenol is Allergens.

Fragrance Chemical	21 CFR	IID	Other
	177: INDIRECT FOOD ADDITIVES: POLYMERS § 177.2800 - Textiles and textile fibers. 184: DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE § 184.1257 - Clove and its derivatives. Eugenol was granted GRAS status by FEMA (1965) and is approved by the FDA as GRAS for food use. The Council of Europe (1974) included eugenol in the list of artificial flavoring substances that may be added to foodstuffs without hazard to public health, giving an ADI of 5 mg/ kg. The Food Chemicals Codex and the United States Pharmacopeia (1965) both have monographs on eugenol. The Joint FAO/WHO Expert Committee on Food Additives has published a monograph and specifications for eugenol giving a conditional ADI of 0-5 mg/kg. **IARC potential carcinogen**	temporary prostheses and the temporary restoration of teeth and cavities.	Eugenol tested at 8% in petrolatum produced a mild irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1971). A patch test using undiluted eugenol for 24 hr produced no reactions in 20 subjects (Katz, 1946). In a test on 21 patients suffering from various dermatoses, several essential oils and their constituents, including eugenol, were tested and produced positive patch-test reactions (Woeber & Krombach, 1969). **Eugenol causes allergic contact dermatitis** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3794103/ During a five-year period 3,065 patients with contact dermatitis were patch tested using a specific mix of fragrances. 509 (16.6%) patients were allergic to the fragrance mix, while 258 (8.4%) patients exhibited an allergic reaction to Myroxylon pereirae (balsam of Peru). Between those 509 patients, 157 were patch tested with eight individual substances contained in the fragrance mix: cinnamal, cinnamyl alcohol, eugenol, isoeugenol, geraniol, hydroxycitronellal, alpha-amyl cinnamal and Evernia prunastri (oak moss). The most frequent allergens were isoeugenol 57.9% (91/157), eugenol 55.4% (87/157), cinnamyl alcohol 34.4% (54/157) and Evernia prunastri (oak moss) 24.2% (38/157). ... Turic P et al; Coll Antropol. 2011 Mar;35(1):83-7 (2011) At a concentration higher than 3 mmol/L, eugenol was cytotoxic to /human/ oral mucosal fibroblasts in a concentration- and time-dependent manner. Cell death was associated with intracellular depletion of glutathione (GSH). ... In addition, eugenol decreased cellular ATP level in a concentration- and time-dependent manner. Eugenol also inhibited lipid peroxidation. ... The IC50 of eugenol on xanthine oxidase activity was about 0.3 mmol/L. No DNA strand break activity for eugenol was found at concentrations between 0.5 and 3 mmol/L. Jeng JH et al; J Dent Res 73 (5): 1050-5 (1994) **DrugBank Interactions** **Target: Estrogen receptor alpha, Estrogen receptor beta, Androgen receptor (See PubChem)**

Fragrance Chemical	21 CFR	IID	Other
Evernia Prunastri (Oakmoss) Extract extract of the aerial parts of the oakmoss, evernia prunastri, usneaceae oils, oakmoss-resinoid evernia prunastri lichen 90028-68-5 9000-50-4 68917-10-2 Contains evernic acid (537-09-7) and usnic acid (125-46-2).	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.510 - Natural flavoring substances and natural substances used in conjunction with flavors.	Not Listed	No pubchem lising for Evernia Prunastri Extract Evernic Acid: https://pubchem.ncbi.nlm.nih.gov/compound/10829 usnic acid: https://pubchem.ncbi.nlm.nih.gov/compound/5646 Sensitization Limits / concerns on atranol and chloroatranol content Taken orally, usnic acid can be toxic and has been linked to instances of clinically apparent, acute liver injury Food and Cosmetics Toxicology. Vol. 13, Pg. 891, 1975.
Formic acid, phenylmethyl ester benzyl formate phenylmethyl formate 104-57-4	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Benzyl formate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) listed benzyl formate, giving an ADI of 5 mg/kg.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/7708 R 21/22 - Harmful in contact with skin and if swallowed. S 24 - Avoid contact with skin. Acute toxicity, Dermal (Category 3), H311 H311 - Toxic in contact with skin P302 + P352 - IF ON SKIN: wash with plenty of soap and water. Food and Cosmetics Toxicology, Vol. 11, Pg. 1019, 1973. **Dermal Toxicity:** The acute dermal L D 50 in rabbits was found to be 2.0 ml/kg (1.3-3.0 ml/kg) (Shelanski & Moldovan, 1971). http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/296.pdf Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ GENOTOXICITY (in vitro) EFSA Study published in Japanese with English abstract. Data extracted from tables. Validity of the study cannot be evaluated. A weak positive result (i.e. 4 mm≤ D<8 mm).was reported (D=4 mm). No information on the use of metabolic Activation

Fragrance Chemical	21 CFR	IID	Other
			Yoo. Y.S., 1986. Mutagenic and antimutagenic activities of flavoring agents used in foodstuffs. Osaka City Med. J. 34(3-4). 267-288. (In Japanese) EFSA concluded not genotoxic in foods at current use level. Shelanski, M.V., Moldovan, M., 1971d. Acute oral toxicity study. Benzyl formate. Food and Drug Research Laboratories, Inc. IBL no. 30357-F. 26 November 1971. Unpublished data submitted by EFFA to FLAVIS Secretariat.
Gamma-Nonalactone nonano-1,4-lactone 5-pentyloxolan-2-one 104-61-0	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. γ-Nonalactone was given GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1974) listed γ-nonalactone, giving an ADI of 1.25 mg/kg. The Food Chemicals Codex (1972) has a monograph on γ-nonalactone and the Joint FAO/ WHO Expert Committee ou Food Additives (1967) has published a monograph and specifications, giving it an unconditional ADI of 0 - 1.25 mg/kg.	Not Listed.	https://pubchem.ncbi.nlm.nih.gov/compound/7710#section=GHS-Classification **A skin irritiant.** Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 979 **Xi – Irritant** **H315 (50%): Causes skin irritation** **H319 (100%): Causes serious eye irritation** **H335 (66.67%): May cause respiratory irritation** Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 2, Pg. 327, 1964. Food and Cosmetics Toxicology. Vol. 13, Pg. 889, 1975. Gigiena Truda i Professional'nye Zabolevaniya. Labor Hygiene and Occupational Diseases. Vol. 18(11), Pg. 40, 1974. γ-Nonalactone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1972). European Journal of Toxicology and Environmental Hygiene. Vol. 9, Pg. 99, 1976.
Gamma-Undecalactone undecano-1,4-lactone	FDA PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/7714 Cosmetic Uses: masking agents perfuming agents

Fragrance Chemical	21 CFR	IID	Other
104-67-6	Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. Reported to be found in apricots, peaches, milk products, meat and passion fruits (Centraal Instituut Voor Voldingsonderzolk, 1973). γ-Undecalactone was given GRAS status by FEMA (1965), is approved by the FDA for food use and is listed by the Council of Europe (1974) with an ADI of 1.25 mg/kg. The Food Chemicals Codex (1972) has a monograph on γ-undecalactone and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications, giving an unconditional ADI of 0-1.25 mg/kg.		solvents Xi – Irritant S 26 - In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. Skin irritation (Category 2), H315 Eye irritation (Category 2A), H319 Specific target organ toxicity - single exposure (Category 3), Respiratory system, H335 Food and Cosmetics Toxicology. Vol. 2, Pg. 327, 1964. Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
Geraniol trans-3,7-dimethyl-2,7-octadien-1-ol Lemonol 106-24-1	FDA PART 182 – SUBSTANCES GENERALLY RECOGNIZED AS SAFE Subpart A--General Provisions Sec. 182.60 Synthetic flavoring substances and adjuvants. Geraniol has been reported in over 250 essential oils (Bedoukian, 1967; Gildemeister & Hoffman, 1960). Geraniol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) listed geraniol, giving an ADI of 5 mg/kg. The Food Chemicals Codex (1972) has a monograph on geraniol.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/637566#section=Top Xi – Irritant R 36/38 - Irritating to skin and eyes. R 41 - Risk of serious damage to eyes. R 43 - May cause sensitisation by skin contact. Skin irritation (Category 2), H315 Skin sensitisation (Category 1), H317 H317 - May cause an allergic skin reaction Food and Cosmetics Toxicology. Vol. 2, Pg. 327, 1964. Food and Cosmetics Toxicology. Vol. 12, Pg. 881, 1974. Sapporo Igaku Zasshi. Sapporo Medical Journal. Vol. 3, Pg. 73, 1952. Hypersensitivity to geraniol may be encountered in certain individuals (Keil, 1947). Geraniol in a concentration of 10% in vaseline gave two positive reactions among 15 cases sensitive to balsams of Peru (Hjorth, 1961). Established Pharmacologic Class [EPC] Standardized Chemical Allergen

Fragrance Chemical	21 CFR	IID	Other
			Physiologic Effects [PE] Increased Histamine Release Physiologic Effects [PE] Cell-mediated Immunity Allergens A severe human skin irritant. Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 1440 Hagvall L et al: Contact Dermatitis 67 (1): 20-7 (2012) In human patch test, geraniol @ 32% concn was severely irritating & geranyl acetate mildly irritating. Motoyoski et al: Cosmet Toiletries 94(8): 41 (1979)
Geranyl Acetate trans-3,7-dimethyl-2,6-octadien-1-yl ethanoate 105-87-3	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.60 - Synthetic flavoring substances and adjuvants. 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.60 - Synthetic flavoring substances and adjuvants. Geranyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) listed geranyl acetate, giving an ADI of 5 mg/kg. The Food Chemicals Codex (1972) has a monograph on geranyl acetate and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for the ester giving a conditional ADI of 0-5 mg/kg.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/1549026 Xi – Irritant H317 (15.29%): May cause an allergic skin reaction R 36/38 - Irritating to skin and eyes. S 24/25 - Avoid contact with skin and eyes. Skin irritation (Category 2), H315 Eye irritation (Category 2A), H319 Specific target organ toxicity - single exposure (Category 3), Respiratory system, H335 Moderate Oral Tox Gosselin, R.E., H.C. Hodge, R.P. Smith, and M.N. Gleason. Clinical Toxicology of Commercial Products. 4th ed. Baltimore: Williams and Wilkins, 1976., p. II-168 Hypersensitivity has been encountered in some individuals (Keil, 1947). H317 (15.29%): May cause an allergic skin reaction H315 (15.29%): Causes skin irritation In human patch test, geraniol @ 32% concn was severely irritating & geranyl acetate mildly irritating. Motoyoski et al: Cosmet Toiletries 94(8): 41 (1979) Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/

Fragrance Chemical	21 CFR	IID	Other
Heliotropine Piperonal 3,4- methylenedioxybenzaldehyde. 120-57-0 30024-74-9	1310: RECORDS AND REPORTS OF LISTED CHEMICALS AND CERTAIN MACHINES; IMPORTATION AND EXPORTATION OF CERTAIN MACHINES § 1310.04 - Maintenance of records. 582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.60 - Synthetic flavoring substances and adjuvants. 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.60 - Synthetic flavoring substances and adjuvants. Heliotropin was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) listed heliotropin giving an ADI of 2.5 mg/kg. The Food Chemicals Codex (1972) has a monograph on heliotropin and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for heliotropin giving an unconditional ADI of 0-2.5 mg/kg.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/8438 Cosmetic Uses: masking agents perfuming agents skin conditioning Xi – Irritant R 36/37/38 - Irritating to eyes, respiratory system, and skin. S 02 - Keep out of the reach of children. S 24/25 - Avoid contact with skin and eyes. Skin irritation (Category 2). H315 A patch test using heliotropin full strength for 24 hr produced one irritation reaction in 20 subjects (Katz, 1946). European Food Safety Authority (efsa) http://www.efsa.europa.eu/ Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 2. Pg. 327. 1964.
Hex-3-en-1-yl acetate 3-hexenyl acetate cis-3-Hexenyl acetate aleol acetate 1708-82-3 3681-71-8	**Could not locate in CFR or an IFRA Standard** ds-3-Hexenyl acetate was granted GRAS status by FEMA (1971). Occurrence: Reported to occur in tea leaves and *Achillea fragrantissima*. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/en/efsajournal/pub/709 http://www.efsa.europa.eu/en/efsajournal/pub/4559	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/5363388#section=Top S 24/25 - Avoid contact with skin and eyes. Little to no safety info Food and Cosmetics Toxicology. Vol. 13. Pg. 454. 1975. Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/

Fragrance Chemical	21 CFR	IID	Other
Hexamethylindanopyran Multiple chemicals and derivatives meet this name. Need more specific information Likely galaxolide (info here assumes Galaxolide)[4] 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran 1222-05-5	**Could not locate in CFR or an IFRA Standard.**	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/91497#section=Top Xi - Irritant. R 38 - Irritating to skin. 1 BioActive Assay Result (ESR1 - estrogen receptor 1 (human). Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Human and Environmental Risk Assesment of HHCB (1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran and related isomers (October 2004). Report Available from: http://www.heraproject.com/RiskAssessment.cfm?SUBID=29 The interaction of HHCB ... with the estrogen receptor (ER), androgen receptor (AR), and progesterone (PR) receptor, using sensitive and specific reporter gene cell lines was assessed. ... HHCB was found to be an antagonist toward the ERbeta, AR and PR. Schreurs RH et al; Toxicol Sci 83 (2):264-72 (2004) Abstract: http://www.ncbi.nlm.nih.gov/pubmed/15537743?dopt=Abstract Galaxolide and Tonalide can bind to and stimulate human estrogen receptor when tested by in vitro methods (Seinen 1999). Both musks were also shown to affect the androgen and progesterone receptors in reporter gene bioassays (Schreurs 2005). Deutsche Lebensmittel - Rundschau. Vol. 94, Pg. 268, 1998. Fragrance chemicals on the ChemSec SIN List https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-on-the-chemsec-sin-list/
Hexyl caproate hexyl hexanoate	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/22873 Xi – Irritant

[4] GALAXOLIDE 50 DEP was replaced by GALAXOLIDE 50 BB in August, 2008 according to Exhibit 3 "CHANGES TO JOHNSON'S BABY POWDER FRAGRANCE INGREDIENTS"

Fragrance Chemical	21 CFR	IID	Other
6378-65-0	§ 172.515 - Synthetic flavoring substances and adjuvants. Hexyl hexanoate is found in alcoholic beverages. Hexyl hexanoate is used in fruit flavoring. Hexyl hexanoate is present in many fruits, Parmesan cheese, alcoholic beverages and black tea. Hexyl hexanoate is a volatile component from fruit ripening.		R 36/38 - Irritating to skin and eyes. S 24/25 - Avoid contact with skin and eyes. Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/709.pdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2013.3169/epdf
Hydroxycitronellal 3,7-dimethyl-7-hydroxyoctanal 107-75-5	FDA PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants. Hydroxycitronellal was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) listed hydroxycitronellal, giving an ADI of 2.5 mg/kg. The Food Chemicals Codex (1972) has a monograph on hydroxycitronellal. Hydroxycitronellal is approved by the FDA for use within allergenic epicutaneous patch tests which are indicated for use as an aid in the diagnosis of allergic contact dermatitis (ACD) in persons 6 years of age and older. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/709.pdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2164/epdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/7888 Xi – Irritant R 36/38 - Irritating to skin and eyes. R 41 - Risk of serious damage to eyes. R 43 - May cause sensitisation by skin contact. Skin irritation (Category 2), H315 Skin sensitisation (Category 1), H317 Eye irritation (Category 2A), H319 H317 - May cause an allergic skin reaction Food and Cosmetics Toxicology. Vol. 12, Pg. 921, 1974. patch test using full strength hydroxycitronellal for 24 hr produced two irritation reactions in 22 subjects (Katz, 1946). EPA Safer Chemical Hydroxycitronellal - Yellow triangle - The chemical has met Safer Choice Criteria for its functional ingredient-class, but has some hazard profile issues. Specifically, a chemical with this code is not associated with a low level of hazard concern for all human health and environmental endpoints. PHARMACOLOGY Target Classification: Transient Receptor Potential Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/

Fragrance Chemical	21 CFR	IID	Other
	http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2010.1453/epdf		Fragrance allergens in 'specific' cosmetic products. Contact Dermatitis. 2011 Apr:64(4):212-9 A stronger patch test elicitation reaction to the allergen hydroxycitronellal plus the irritant sodium lauryl sulfate. Contact Dermatitis. 2003 Sep:49(3):133-9.
Isoamyl Acetate Amyl acetate β-methyl butyl acetate isopentyl acetate 123-92-2	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Isopentyl acetate is found in apple. Isopentyl acetate is present in many fruit aromas, especially banana. Isopentyl acetate is used in banana flavoring. Isoamyl acetate has a strong odor (similar to Juicy Fruit or a pear drop) which is also described as similar to both banana and pear. Banana oil is a term that is applied either to pure isoamyl acetate or to flavorings that are mixtures of isoamyl acetate, amyl acetate, nitrocellulose and other flavors. Isoamyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1974) listed isoamyl acetate, giving an ADI of 1 mg/kg. The Food Chemicals Codex (1972) has a monograph on isoamyl acetate and Browning (1965) has an extensive monograph on amyl acetate. Threshold limit value. The threshold limit value for isoamyl acetate has been set at 100 ppm (American Conference of Governmental Industrial Hygienists, 1973). Registry of Toxic Effects of Chemical Substances (RTECS)	Approved in 1 drug for oral administration (suspension) at a concentration 1 mg/10mL	https://pubchem.ncbi.nlm.nih.gov/compound/31276 **Xi – Irritant** **H315: Causes skin irritation** **R 66 - Repeated exposure may cause skin dryness or cracking.** **H319: Causes serious eye irritation** **H372: Causes damage to organs through prolonged or repeated exposure** **Repeated exposure may cause skin dryness or cracking.** **Cosmetic Uses:** **masking agents** **perfuming agents** **solvents** Overexposure to isoamyl acetate may cause irritation of the eyes, nose, and throat. Mackison, F. W., R. S. Stricoff, and L. J. Partridge, Jr. (eds.). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS(NIOSH) Publication No. 81-123 (3 VOLS). Washington, DC: U.S. Government Printing Office, Jan. 1981., p. 1 Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Isoamyl acetate is a central nervous depressant Gosselin, R.E., R.P. Smith, H.C. Hodge. Clinical Toxicology of Commercial Products. 5th ed. Baltimore: Williams and Wilkins. 1984., p. II-202 vapor is known to irritate eyes, skin and respiratory tract, and to cause mild unspecific central nervous system symptoms. Baumann CR et al; J Neurol 255(5):762-3 (2008)

Fragrance Chemical	21 CFR	IID	Other
	https://www.cdc.gov/niosh-rtecs/NS958940.html European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/204.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/643.pdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2010.1400/epdf		
Juniperus Communis Fruit Oil Volatile oil obtained from the berries of the juniper, juniperus communis l., cupressaceae 8012-91-7 73049-62-4 84603-69-0	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). Juniper berry was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included juniper berry in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The Food Chemicals Codex (1972) has a monograph on juniper berry.	Not Listed	No PubChem monograph R 38 - Irritating to skin. R 43 - May cause sensitisation by skin contact. R 65 - Harmful: may cause lung damage if swallowed. Skin irritation (Category 2), H315 Rat Oral Tox: Pharmazie. Vol. 14, Pg. 435, 1959. Undiluted juniper berry oil applied to the backs of hairless mice and swine was not irritating (Urbach & Forbes, 1972), but applied to intact or abraded rabbit skin for 24 hr under occlusion it was moderately irritating (Shelanski, 1972). A patch test using juniper berry full strength for 24 hr produced two irritation reactions in 20 subjects (Katz, 1946). Cosmetic Uses: masking agents perfuming agents Six of the 86 subjects were sensitive to Juniper Berry Oil (Rudzki and Grzywa 1986). Int J Toxicol. 2001:20 Suppl 2:41-56. Final report on the safety assessment of Juniperus communis Extract, Juniperus oxycedrus Extract, Juniperus oxycedrus Tar, Juniperus phoenicea extract, and Juniperus virginiana Extract.

Fragrance Chemical	21 CFR	IID	Other
			Juniperus Communis Extract did affect fertility and was abortifacient in studies using albino rats, but was not teratogenic. **... dermal reproductive/developmental toxicity data (to include determination of a no-effect level); two genotoxicity assays (one in a mammalian system) for each extract; if positive, a 2-year dermal carcinogenicity assay performed using National Toxicology Program (NTP) methods is needed; a 2-year dermal carcinogenicity assay performed using NTP methods on Juniperus Oxycedrus Tar; and irritation and sensitization data on each extract and the tar (these data are needed because the available data on the oils cannot be extrapolated). Until these data are available, it is concluded that the available data are insufficient to support the safety of these ingredients in cosmetic formulations.**
Lavandula Angustifolia (Lavender) Oil essential oil distilled from the flowering herbs of the lavender, lavandula angustifolia, labiatae The main constituent of lavender oil is linalyl acetate (Guenther, 1949). 90063-37-9 8000-28-0	FDA PART 182 -- SUBSTANCES GENERALLY RECOGNIZED AS SAFE Subpart A--General Provisions Sec. 182.20 Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). 341: COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTIASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE § 341.40 - Permitted combinations of active ingredients. Lavender oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included lavender oil in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. Both the Food Chemicals Codex (1972) and the National Formulary (1970) have monographs on lavender oil.	Not listed in IID but permitted in one product up to 4 mg as a nasal inhaler (see 21 CFR Part 341)	No PubChem monograph R 36/38 - Irritating to skin and eyes. R 43 - May cause sensitisation by skin contact. Food and Cosmetics Toxicology. Vol. 14. Pg. 449. 1976. **Nutr Cancer. 2014;66(3):424-34** **Comparative studies of cytotoxic and apoptotic properties of different extracts and the essential oil of Lavandula angustifolia on malignant and normal cells.** **L. angustifolia has cytotoxic and apoptotic effects in HeLa and MCF-7 cell lines, and apoptosis is proposed as the possible mechanism of action.** IFRA Critical Effect: Sensitization Cell Prolif. 2004 Jun;37(3):221-9. Cytotoxicity of lavender oil and its major components to human skin cells. This study has demonstrated that lavender oil is cytotoxic to human skin cells in vitro (endothelial cells and fibroblasts) at a concentration of 0.25% (v/v) in all cell types tested (HMEC-1, HNDF and 153BR).

Fragrance Chemical	21 CFR	IID	Other
Lemon oil terpenes 68917-33-9	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.510 - Natural flavoring substances and natural substances used in conjunction with flavors.	Not Listed	PuBChem Not Found IFRA Use Restriction due to Phototoxicity http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMymqUl
Linalool Coriandrol 3,7-dimethyl-1,6-octadien-3-ol 78-70-6 Found in allspice and over 200 essential oils. Present in numerous fruits.	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.60 - Synthetic flavoring substances and adjuvants. 172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.60 - Synthetic flavoring substances and adjuvants. No safety concern at current levels of intake when used as a flavouring agent. The 1979 group ADI of 0-0.5 mg/kg bw for citral, geranyl acetate, citronellol, linalool, and linalyl acetate, expressed as citral, was maintained at the fifty-first (TRS 891/90, 1998) and sixty-first (TRS for JECFA 61 in press) meetings. **Registry of Toxic Effects of Chemical Substances (RTECS)** https://www.cdc.gov/niosh-rtecs/RG581E98.html **Skin and Eye Irritation and References** **Mutation Data and Reference** **Reproductive Effects Data and References** 100microLiters produced moderate irritation in rabbit eye	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/6549#section=Top Xi – Irritant H315 (96.96%): Causes skin irritation [Warning Skin corrosion/irritation] H317 (53.26%): May cause an allergic skin reaction [Warning Sensitization, Skin] H319 (77.71%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] 20 Active BioAssay results IFRA Use Restriction Sensitization http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMymqUl Dermal Systemic Exposure in Cosmetic Products: 6.3236 mg/kg/day (IFRA, 2002) Linalool may permeate porcine (and by extension also human) buccal mucosa in function of its concentration (14.46% w/w) and of formulation /as in the essential oil of Salvia desoleana Atzei & Picci/ Organization for Economic Cooperation and Development: Screening Information Data Set for LINALOOL (78-70-6) p.95 (March 2002). http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html Effects of Long Term Exposure: may have effects on the liver. http://www.ilo.org/dyn/icse/showcard.display?p_version=2&p_card_id=0912 Linalool at concentrations up to 20% was consistently found not to be a sensitizer in human maximization tests. It was not phototoxic or photoallergenic in human tests. Linalool can cause

Fragrance Chemical	21 CFR	IID	Other
	European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/331.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/978.pdf Linalool was given GRAS status by FEM A (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) listed linalool giving an ADI of 0.25 mg/kg. The Food Chemicals Codex (1972) has a monograph on linalool and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for linalool giving a conditional ADI of 0-0.25 mg/kg.		allergic contact dermatitis. Linalool was not genotoxic when tested in vitro by the micronucleus test on peripheral human lymphocytes. Lavender (Lavandula angustifolia) oil, chiefly composed of linalyl acetate (51%) and linalool (35%), is considered to be one of the mildest of known plant essential oils and has a history in wound healing. Concerns are building about the potential for irritant or allergenic skin reactions with the use of lavender oil. This study has demonstrated that **lavender oil is cytotoxic to human skin cells in vitro** (endothelial cells and fibroblasts) at a concentration of 0.25% (v/v) in all cell types tested (HMEC-1, HNDF and 153BR). Prashar A et al; Cell Prolif 37 (3): 221-9 (2004) Linalol (CAS # 78-70-6) was evaluated for primary eye irritation. The test substance was applied (0.1 mL) to the conjunctive sac of 6 New Zealand white rabbits per concentration at 100%; 30%; 10%; or 3%. Irritation was moderate at 100%, slightly at 30%; very slightly at 10%; and no irritation at 3%. RHONE-POULENC INC; Initial Submission: Letter from Rhone-Poulenc Inc to USEPA Submitting Information on the Enclosed Acute Toxicity and Local Tolerance Report with Linalol and Dehydrolinalol W-Attachments; 09/11/92; EPA No. 88-920006656; Fiche No. OTS0543729 Journal of Scientific and Industrial Research, Section C: Biological Sciences, Vol. 21, Pg. 342, 1962. Food and Cosmetics Toxicology. Vol. 2, Pg. 327, 1964. Food and Cosmetics Toxicology. Vol. 13, Pg. 827, 1975. Irritation. Linalool applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Fogleman, 1970). Cytotoxicity. Linalool was found to be **moderately cytotoxic** to Chang, HeLa, and KB cells (Nachev, Zolotovich, Silyanovska & Stojcev, 1967). When tested against HeLa cells in monolayer culture, linalool was cytotoxic at 100 ug/litre, weakly active at 10 ug/litre, and inactive at 1 ug/litre (Nachev, Zolotovitch, Siljanowski & Stojcev, 1968).
Linalyl Acetate	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/8294

Fragrance Chemical	21 CFR	IID	Other
1,6-octadien-3-ol, 3,7-dimethyl-, acetate 115-95-7 Found in cardamom and is isolated from numerous plants and essential oils, e. g. clary sage, lavender, lemon etc.	§ 582.60 - Synthetic flavoring substances and adjuvants. 172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.60 - Synthetic flavoring substances and adjuvants. **Registry of Toxic Effects of Chemical Substances (RTECS)** https://www.cdc.gov/niosh-rtecs/RG5A2DF0.html https://pubchem.ncbi.nlm.nih.gov/compound/8294#section=NIOSH-Toxicity-Data&fullscreen=true No safety concern at current levels of intake when used as a flavoring agent. The 1979 group ADI of 0-0.5 mg/kg bw for citral, geranyl acetate, citronellol, linalool, and linalyl acetate, expressed as citral, was maintained at the fifty-first (TRS 891/90, 1998) and sixty-first (TRS for JECFA 61 in press) meetings. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/331.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/978.pdf		Xi – Irritant H315 (98.36%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (98.2%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] R 36/38 - Irritating to skin and eyes. 2 Active BioAssay Results Linalyl acetate (100%) appeared to be severely irritating to rabbit skin and moderately irritating to the skin of the guinea pig. In a test with miniature swines, application of 0.05 g linalyl acetate under a patch for 48 hours /caused/ no irritation Organization for Economic Cooperation and Development; Screening Information Data Set for LINALYL ACETATE (115-95-7) p.11 (March 2002). http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Absorbed through the skin Jager W et al; Journal of Soc Cosmet Chem 43: 49-54 (1992) Letizia CS et al; Food Chem Toxicol 41 (7): 965-76 (2003) The potential genotoxicity of linalyl acetate, was evaluated in vitro by the micronucleus test on peripheral human lymphocytes. In the range of non-toxic concentrations (0.5-100 ug/mL), linalyl acetate increased the frequency of micronuclei significantly and in concentration-dependent manner. **slightly increase the number of skin papillomas and carcinomas compared to benzo(a)pyrene controls** Organization for Economic Cooperation and Development; Screening Information Data Set for LINALYL ACETATE (115-95-7) p.13 & 51 (March 2002). Available from, as of July 14, 2008: http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html FCTXAV 13,827,1975 Toksikologicheskii Vestnik. Vol. (5). Pg. 41, 1994

Fragrance Chemical	21 CFR	IID	Other
			Implication of limonene and linalyl acetate in cytotoxicity induced by bergamot essential oil in human neuroblastoma cells. Fitoterapia. 2013 Sep:89:48-57. Genotoxicity of lavender oil, linalyl acetate, and linalool on human lymphocytes in vitro. Environ Mol Mutagen. 2011 Jan;52(1):69-71. These findings suggest that the mutagenic activity of lavender oil can be related to the presence of linalyl acetate, which seems to have a profile of an aneugenic agent. Autoxidation of linalyl acetate, the main component of lavender oil, creates potent contact allergens. Contact Dermatitis. 2008 Jan;58(1):9-14. Cell Prolif. 2004 Jun:37(3):221-9. Cytotoxicity of lavender oil and its major components to human skin cells. Linalyl acetate cytotoxicity was higher than that of the oil itself
Mentha Arvensis Leaf Oil Corn Mint Oil 68917-18-0 oil derived from the leaves of the horse mint, mentha arvensis l.	**Could not locate in CFR or an IFRA Standard** **Cornmint oil is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the Food Chemicals Codex (1972).**	Not Listed	PubChem Not Found Cosmetic Uses: masking agents R 41 - Risk of serious damage to eyes. S 24/25 - Avoid contact with skin and eyes. Not for fragrance use according to Good Scents In an evaluation of **skin-penetrating agents**, "Oleum Menthae" increased deep penetration of Rhodamine Â into the corium and subcutis of guinea-pig skin, while "peppermint oil" and "Oleum Menthae piperitae" caused only a slight increase in penetration (Meyer, 1965). The essential **oil of M. arvensis produced moderate cytotoxic effects**, which could not be attributed to its content of menthol (85%) and related menthyl compounds (Siljanowska, Stojcev, Zolotovitch & Nachev, 1969). Food and Cosmetics Toxicology, Vol. 13, Pg. 771, 1975.
Menthyl Acetate	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/27867 Fragrance Chemicals of Concern Present on the IFRA List 2015:

Fragrance Chemical	21 CFR	IID	Other
cyclohexanol, 5-methyl-2-(1-methylethyl)-, acetate, (1R,2S,5R)- Neomenthyl acetate 89-48-5 Found in peppermint oil (Guenther, 1949).	§ 582.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). 172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). Menthyl acetate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR. 121.1164). The Council of Europe (1974) listed menthyl acetate giving an ADI of 2 mg/kg (therapeutic doses). Flavor & Extract Manufacturers Association (FEMA) reference(s): http://www.thegoodscentscompany.com/epis ys/ep1046271.html		https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Xi - Irritant R 36/38 - Irritating to skin and eyes. S 24/25 - Avoid contact with skin and eyes. Menthyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Shelanski, 1972). Cosmetic Uses: masking agents refreshing agents
Methyl 2-(methylamino)benzoate **Dimethyl Anthranilate** 2-Methylaminobenzoic Acid Methyl Ester 85-91-6 Found as the main constituent in oil of mandarin leaves, and as a minor constituent in oils of mandarin, petitgrain, hyacinth and rue	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Dimethyl anthranilate was given GRAS status by FEM A (1965) and is approved by the FDA for food use. The Council of Europe (1974) included dimethyl anthranilate in the list of flavoring substances that may be added temporarily to foodstuffs without hazard to public health. The Food Chemicals Codex (1972) has a monograph on dimethyl anthranilate. Joint FAO/WHO Expert Committee on Food Additives set an ADI of 0.2 mg/kg in 2005.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/6826 H315 (80.56%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (94.44%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] Xi - Irritant R 36/38 - Irritating to skin and eyes. R 43 - May cause sensitisation by skin contact. 1 Active BioAssay Result IFRA Use Restriction for Phototoxicity and potential for nitrosam http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl limits in the finished product for - "leave on the skin contact": 0.1000 % Restriction.

Fragrance Chemical	21 CFR	IID	Other
	European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/856.pdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2441/epdf		IFRA fragrance material specification: For applications on areas of the skin exposed to sunlight, excluding bath preparations, soaps and other wash-off products, limit to 10% in the finished cosmetic product. Based on the phototoxic potential and on the observed no-effect level of approximately 2 mg/cm2 of the hairless mouse (Food and Chemical Toxicology 17, 273 (1979)). The material has been identified for having the potential of forming nitrosamines in nitrosating systems. **Downstream users therefore have to be notified of the presence of the material and its potential to be able to consider adequate protective measures.** Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 8, Pg. 359, 1970. U.S. Army Armament Research & Development Command, Chemical Systems Laboratory, NIOSH Exchange Chemicals. Vol. NX#07000 Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced two questionable sensitization reactions (Kligman, 1974; see Preface Note no. 1). When the material was retested (Kligman, 1966) on a different panel of 25 volunteers at a concentration of 10% in petrolatum, it produced no sensitization reactions (Kligman, 1974). Phototoxicity. Dimethyl anthranilate tested at a concentration of 5% in hydrophilic ointment produced **phototoxic effects on 8 out of 10 human subjects** (Kaidbey, 1978). Undiluted dimethyl anthranilate produced phototoxic effects on the skin of the hairless mouse (Forbes, Urbach & Davies, 1978).
Methyl Anthranilate benzoic acid, 2-amino-, methyl ester 134-20-3	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.60 - Synthetic flavoring substances and adjuvants.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/8635#section=Top H319 (100%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] Xi - Irritant R 36/38 - Irritating to skin and eyes.

Fragrance Chemical	21 CFR	IID	Other
Reported to be found in nearly 50 essential oils, including neroli, orange, bergamot, lemon, mandarin, jasmine, tuberose, gardenia, champaca, ylang-ylang and others; also found in the juice and oil of Vitis lahrusca (Gildemeister & Hoffman, 1966).	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.60 - Synthetic flavoring substances and adjuvants. Methyl anthranilate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) listed methyl anthranilate, giving an ADI of 1.5 mg/kg. It is the subject of a Food Chemicals Codex (1972) monograph and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for methyl anthranilate, giving a conditional ADI of 0-1.5 mg/kg. ADI reaffirmed in 2005.		10 Active BioAssay Results Irritation. Methyl anthranilate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 2, Pg. 327, 1964. Food and Cosmetics Toxicology. Vol. 12, Pg. 935, 1974. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/856.pdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2441/epdf
Methyl Benzoate benzoic acid methyl ester 93-58-3 Methyl benzoate is found in allspice and is present in various flower oils, banana, cherry, pimento berry, ceriman (Monstera deliciosa), clove bud and stem, mustard, coffee, black tea, dill, starfruit and cherimoya (Annona cherimola).	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Methyl benzoate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) listed methyl benzoate giving an ADI of 5 mg/kg. Both the Food Chemicals Codex (1972) and Browning (1965) have monographs on methyl benzoate. Registry of Toxic Effects of Chemical Substances (RTECS) https://www.cdc.gov/niosh-rtecs/DH3ABF10.html		https://pubchem.ncbi.nlm.nih.gov/compound/7150#section=Skin-Eye-and-Respiratory-Irritations R 36/38 - Irritating to skin and eyes. R 42/43 - May cause sensitization by inhalation and skin contact. limits in the finished product for - "leave on the skin contact": 0.5000 % Recommendation. 3 Active BioAssay Results Irritates the eyes, skin, and respiratory tract. Pohanish, R.P. (ed). Sittig's Handbook of Toxic and Hazardous Chemical Carcinogens 6th Edition Volume 1: A-K,Volume 2: L-Z. William Andrew, Waltham, MA 2012, p. 1761 In nonoccluded skin irritation test carried out on clipped rabbits, no signs of erythema were observed in any of the animals (14/14), 4 and 24 hr after the application of 0.5 mL undiluted methyl benzoate. Very slight erythema was observed in the remaining

Fragrance Chemical	21 CFR	IID	Other
	European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/296.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/637.pdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1025/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2176/epdf		(12/12) rabbits 24 hr after a second application. **Redness increased with successive treatments**. Moderate to severe edema was observed in animals (4/4) receiving 6 applications. **May cause skin sensitization and allergy. May cause an asthma-like allergy**. Can affect the nervous system causing tremors and muscle weakness. Pohanish, R.P. (ed). Sittig's Handbook of Toxic and Hazardous Chemical Carcinogens 6th Edition Volume 1: A-K,Volume 2: L-Z. William Andrew. Waltham, MA 2012. p. 1761 Percutaneous absorption. Methyl benzoate was slow to penetrate the skin of rats (Valette & Cavier, 1954). The authors concluded that methyl benzoate not only **caused toxic effects to the cells but also promoted membrane penetration by other substances.** **Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 31(suppl. 3): 342S-372S (2012). Available from, as of July 2, 2015:** http://www.ctfa.org/ingredients Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 12. Pg. 937. 1974. Journal of Pharmacology and Experimental Therapeutics. Vol. 84. Pg. 358. 1945.
Methyl Cinnamate methyl 3-phenylprop-2-enoate 103-26-4 Found in Basil. Occurs in essential oils e.g. from Ocimum and Alpinia spp. Also present in various fruits, e.g. guava, feijoa, strawberry.	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.60 - Synthetic flavoring substances and adjuvants. 172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.60 - Synthetic flavoring substances and adjuvants.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/637520#section=Top Xi - Irritant R 36/38 - Irritating to skin and eyes. H317 (100%): May cause an allergic skin reaction [Warning Sensitization, Skin] Dermal Systemic Exposure in Cosmetic Products: 0.0054 mg/kg/day (IFRA, 2001) Irritation. Methyl cinnamate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Weir, 1971), and the ester produced no conjunctival irritation in the rabbit eye (Weir, 1971).

Fragrance Chemical	21 CFR	IID	Other
	Methyl cinnamate was given GRAS status by FEM A (1965) and is approved by the FDA for food use. The Council of Europe (1974) listed methyl cinnamate, giving an ADI of 1.25 mg/kg. The Food Chemicals Codex (1972) has a monograph on methyl cinnamate. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2017.4672/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1032/epdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/733.pdf		Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Chemical composition of the essential oil from basil (Ocimum basilicum Linn.) and its in vitro cytotoxicity against HeLa and HEp-2 human cancer cell lines and NIH 3T3 mouse embryonic fibroblasts. Nat Prod Res. 2012;26(12):1112-8. The major constituents were found to be methyl cinnamate (70.1%), linalool (17.5%), β-elemene (2.6%) and camphor (1.52%). Basil oil has potent cytotoxicity. The absorption and metabolism of methyl cinnamate. Toxicology. 1977 Feb;7(1):123-32. Food and Cosmetics Toxicology. Vol. 13, Pg. 849, 1975. Food Chem Toxicol. 2007;45 Suppl 1:S113-9.
Methyl Hydrogenated Rosinate Methyl ester of rosin (partially hydrogenated) 8050-15-5	Methyl Hydrogenated Rosinate Not Found although it has an FDA UNII. Providing info for Methyl ester of rosin (partially hydrogenated), which appears to be the same or very similar. 172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. § 172.615 - Chewing gum base. Methyl ester of rosin (partially hydrogenated) has been approved by the FDA for food use. The Food Chemicals Codex (1972) has a monograph on methyl ester of rosin (partially hydrogenated).	Not Listed	PubChem not found Cosmetic Uses: film formers perfuming agents skin conditioning Useful as a perfumery solvent rather than an aromatic ingredient Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
Methyl Salicylate Wintergreen Oil benzoic acid, 2-hydroxy-, methyl ester	310: NEW DRUGS § 310.531 - Drug products containing active ingredients offered over-the-counter (OTC) for the treatment of boils.	Approved in 3 drug products for oral admin up to 16 mg.	https://pubchem.ncbi.nlm.nih.gov/compound/4133 H315 (23.08%): Causes skin irritation [Warning Skin corrosion/irritation]

Fragrance Chemical	21 CFR	IID	Other
119-36-8 Present in white wine, tea, porcini mushroom Boletus edulis, Bourbon vanilla, clary sage, red sage and fruits including cherry, apple, raspberry, papaya and plum. Methyl 2-hydroxybenzoate is found in leaves of Gaultheria procumbens (wintergreen). For acute joint and muscular pain, methyl salicylate is used as a rubefacient and analgesic in deep heating liniments (ie Salonpas). It is used as a flavoring agent in chewing gums and mints in small concentrations and added as antiseptic in mouthwash solutions.	§ 310.544 - Drug products containing active ingredients offered over-the-counter (OTC) for use as a smoking deterrent. § 310.545 - Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses. 341: COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTIASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE § 341.40 - Permitted combinations of active ingredients. 369: INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER-THE-COUNTER SALE § 369.20 - Drugs; recommended warning and caution statements. 201: LABELING § 201.303 - Labeling of drug preparations containing significant proportions of wintergreen oil. § 201.314 - Labeling of drug preparations containing salicylates. 172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. 2001 Flavor ADI: 0-0.5 mg/kg bw (1967) **Registry of Toxic Effects of Chemical Substances (RTECS)** https://www.cdc.gov/niosh-rtecs/VO481908.html **Severe eye and skin irratation in guinea pig**		H319 (28.56%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] R 36/38 - Irritating to skin and eyes. 7 Active BioAssay Results maximum skin levels for fine fragrances: 0.2900 % and are based on the assumption that the fragrance mixture is used at 20% in a consumer product (IFRA Use Level Survey). (IFRA, 2002) use level in formulae for use in cosmetics: 0.1300 % Restrictricted from Fragrance use In Canada. Dermal Systemic Exposure in Cosmetic Products: 0.0034 mg/kg/day (IFRA, 2002) Approximately 12-20% of topically applied methyl salicylate may be systemically absorbed through intact skin within 10 hours of application, and absorption varies with different conditions such as surface area and pH. **Dermal bioavailability is in the range of 11.8 – 30.7%.** After absorption, methyl salicylate is distributed throughout most body tissues and most transcellular fluids, primarily by pH dependent passive processes. Salicylate is actively transported by a low-capacity, saturable system out of the CSF across the choroid plexus. **The drug readily crosses the placental barrier.** http://www.drugbank.ca/drugs/DB09543 Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Department of Health & Human Services/National Institute of Environmental Health Sciences, National Toxicology Program; Methyl Salicylate, CAS #119-36-8): Reproduction and Fertility Assessment in CD-1 Mice When Administered by Gavage. NTP Study No. RACB82104 (August 10, 1984): http://ntp.niehs.nih.gov/index.cfm?objectid=0847F35A-0850-D1E7-B02ED4DDD150F990

Fragrance Chemical	21 CFR	IID	Other
	Methyl salicylate is potentially deadly, especially in the pediatric population. Toxic ingestions of salicylates typically occur with doses of approximately 150 mg/kg body weight. This can be achieved with 1 ml of oil of wintergreen. The lowest published lethal dose is 101 mg/kg body weight in adult humans, (or 7.07 grams for a 70 kg adult). It has proven fatal to small children in doses as small as 4 ml. **The estrogenic potential of salicylate esters and their possible risks in foods and cosmetics.** **Toxicol Lett. 2012 Mar 7;209(2):146-53**		European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2176/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1025/epdf American Journal of the Medical Sciences. Vol. 193, Pg. 772, 1937. Food and Cosmetics Toxicology. Vol. 2, Pg. 327, 1964. Food and Cosmetics Toxicology. Vol. 16, Pg. 821, 1978. Journal of Pharmacology and Experimental Therapeutics. Vol. 132, Pg. 207, 1961 Clinical Toxicology. Vol. 6, Pg. 189, 1973. FAO Nutrition Meetings Report Series. Vol. 44A, Pg. 63, 1967. Evaluation of safety for food additives: An illustration involving the influence of methyl salicylate on rat reproduction. Biometrics. 1970 Jun;26(2):181-4.
Myristica Fragrans (Nutmeg) Kernel Oil Nutmeg Oil 8008-45-5 Nutmeg Oil is the essential oil obtained from ground nutmeg. Nutmeg oil is typically used as a food flavoring but also has analgesic properties. https://ncit.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=NCI_Thesaurus&ns=NCI_Thesaurus&code=C107336	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). 310: NEW DRUGS § 310.545 - Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses. 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). 101: FOOD LABELING § 101.22 - Foods; labeling of spices, flavorings, colorings and chemical preservatives. Nutmeg was given GRAS status by FEM A (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974)	Present in 1 Approved Drug product for oral administration (elixir). Dose is 4.5 mg/mL.	https://pubchem.ncbi.nlm.nih.gov/compound/6850746#section=Top Xi – Irritant R 36/38 - Irritating to skin and eyes. R 43 - May cause sensitisation by skin contact. H315 - Causes skin irritation H319 - Causes serious eye irritation IFRA Critical Effect: Sensitization contains the following IFRA (Annex) restricted components: (non-analysis max. level reference only) methyl eugenol Max. Found: <1.00 % and Reason: Potential carcinogenic activity in animals geraniol Max. Found: <0.40 % and Reason: Sensitization citronellol Max. Found: <0.20 % and Reason: Sensitization eugenol Max. Found: <0.60 % and Reason: Sensitization isoeugenol Max. Found: <1.00 % and Reason: Sensitization Recommendation for nutmeg oil usage levels up to: 2.0000 % in the fragrance concentrate. East Indian nutmeg oil ... was **moderately irritating** to rabbit skin when applied undiluted for 24 hr under occlusion.

Fragrance Chemical	21 CFR	IID	Other
	included nutmeg in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. The Food Chemicals Codex (1972) has a monograph on nutmeg oil, which has also been included in extensive studies in the GRAS review program (National Technical Information Service (NTIS) publications PB221-222 & PB221-807).		Leung, A.Y., Foster, S. Encyclopedia of Common Natural Ingredients Used in Food, Drugs, and Cosmetics. New York, NY. John Wiley & Sons, Inc. 1996., p. 386 Cosmetic Uses: masking agents skin conditioning Food and Cosmetics Toxicology. Vol. 17, Pg. 851, 1979. American Journal of Emergency Medicine. Vol. 10, Pg. 429, 1992.
Myroxylon Balsamum (Balsam Tolu) Resin Tolu Balsam Balsam of Tolu 9000-64-0 Oleoresin (balsam tolu) obtained from the bark exudate of balsam tolu tree, myroxylon balsamum Balsam tolu contains approximately 80% resin, together with benzoic and cinnamic acids, benzyl benzoate, benzyl cinnamate, vanillin and a small amount of volatile oil (Poucher, 1974).	310: NEW DRUGS § 310.545 - Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses. 172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.510 - Natural flavoring substances and natural substances used in conjunction with flavors. Balsam tolu was given GRAS status by FEM A (1965) and is approved by the FDA for food use. The Council of Europe (1974) included balsam tolu in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The United States Pharmacopeia (1965) has a monograph on balsam tolu.	Present in 2 drug products for oral administration (tablet and suspension). Dosage is not specified.	PubChem Not Found Xi - Irritant R 43 - May cause sensitisation by skin contact. Cosmetic Uses: film formers hair conditioning masking agents Irritation. Balsam tolu applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Hart, 1971). Sensitization. In patch tests of preparations of brittle balsam tolu carried out on 67 patients allergic to Peru balsam (Hjorth, 1961), positive reactions were obtained in 21% with 5% powdered balsam tolu in vaseline (34 tests), in 100% with Vernix tolutanum Ph.D (three tests), in 50% with 10% balsam tolu in alcohol (ten tests) and in 73% with 1% balsam tolu in alcohol (27 tests). Percutaneous absorption. Tolu balsam oil was not absorbed through the intact skin of mice (Meyer & Meyer, 1959) or guinea-pigs (Meyer, 1965).
Myroxylon Pereirae (Balsam Peru) Oil Peru Balsam Oil Balsam Peru Balsam Of Peru Myroxylon Pereirae Klotzsch Oil	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE	Balsum Peru present in one drug product for rectal administration (Suppository) at 100 mg.	PubChem Not Found Cosmetic Uses: masking agents Xi - Irritant R 38 - Irritating to skin. R 43 - May cause sensitisation by skin contact. IFRA Use Restriction due to Sensitization

Fragrance Chemical	21 CFR	IID	Other
8007-00-9	§ 182.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). Peru balsam was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included Peru balsam in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. Recommendation for peru balsam usage levels up to: **PROHIBITED: Should not be used as a fragrance ingredient.** Do not use on any part of the body because of sensitizing potential. tsca definition 2008: extractives and their physically modified derivatives. it consists primarily of resins, essential oils, and usually cinnamic and benzoic acids. (myroxylon balsamum pereirae, leguminosae). **Fragrance Chemicals on the EU Annex ii: Chemicals prohibited from cosmetics in the EU** https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-prohibited-eu-cosmetics/ **IFRA Prohibited**		http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl IFRA Critical Effect: Sensitization IFRA fragrance material specification: Extracts and distillates of Peru balsam (the exudation from Myroxylon pereirae (Royle) Klotzsch) should not be used such that the total level exceeds 0.4% in cosmetic products. Based on a wide variety of test results on the sensitising potential of Peru balsam and its derivatives. IFRA: View Standard Irritation. Peru balsam applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Lynch, 1971b). **Sensitization**. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and **produced sensitization reactions in seven of those tested** (Kligman, 1971). Peru balsam (8%) was also tested by the repeated insult patch test procedure (Shelanski & Shelanski, 1953), using 15 24-hr exposures in 50 human subjects, without producing sensitization reactions (Shelanski, 1971). Hjorth (1961) reported the incidence of positive reactions to patch tests with Peru balsam **of 5558 patients tested, 6.9% produced a reaction to Peru balsam** (Magnusson, Blohm, Fregert, Hjorth, Hovding, Pirilä & Skog, 1968). Peru balsam was equally involved in both occupational and non-occupational groups and may be **considered a consumer hazard as well as an occupational hazard** Malten, Fregert, Bandmann, Calnan, Cronin, Hjorth, Magnusson, Maibach, Meneghini, Pirilä, & Wilkinson, (1971). Occupational dermatitis in five European dermatological departments. Berufsdermatosen 19, 1. **Allergic reactions to balsam of Peru in feminine hygiene sprays have been reported (Fisher, 1973). Peru balsam is among the most common contact allergens, accounting for 7-9% reactions among 340 patients tested (Baer, Ramsey & Biondi, 1973).** Food and Cosmetics Toxicology, Vol. 12, Pg. 951, 1974.

Fragrance Chemical	21 CFR	IID	Other
Nonan-1-ol Nonyl Alcohol nonanol alcohol C9 143-08-8 28473-21-4 Widespread in nature, occurs in oils of orange, citronella and lemon. Also found in cheese, prickly pears and bread.	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. 176: INDIRECT FOOD ADDITIVES: PAPER AND PAPERBOARD COMPONENTS § 176.210 - Defoaming agents used in the manufacture of paper and paperboard Alcohol C-9 has been granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) listed alcohol C-9 (nonyl alcohol), giving an ADI of 1 mg/kg. The Food Chemicals Codex (1966) has a monograph on alcohol C-9 and an extensive monograph on nonanol has been compiled by Browning (1965). European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2013.3169/epdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/8914#section=GHS-Classification Xi N – Irritant H315 (17.45%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (100%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] Eye irritation (Category 2A), H319 1 Active BioAssay Result Based on the eye irritation scores that were reported, 1-nonanol would be considered an eye irritant using the EU criteria. Skin absorption is low; the dermal flux of 1-nonanol in human skin (epidermis) in vitro is 0.003 mg/sq cm/hr. Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons, New York, N.Y. (2001)., p. 6:481-482 1-Nonanol (2% in petrolatum) was reportedly neither a skin irritant nor a skin sensitizer to humans. Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons, New York, N.Y. (2001)., p. 6:482 Application of 5 mL (1.6 to 2.0 g/kg) of nonyl alcohol to the skin of rabbits for 1 hr/day on each of 50 days over period of 75 days resulted in retarded growth & erythema of the treated skin but no mortality. Clayton, G. D. and F. E. Clayton (eds.). Patty's Industrial Hygiene and Toxicology: Volume 2A, 2B, 2C: Toxicology, 3rd ed. New York: John Wiley Sons, 1981-1982., p. 4629 In rabbits and rats exposed to conc of 0.8, 0.6, or 0.2 mg/L (136, 99, or 33 ppm) nonyl alcohol for 2 hr/day for 2 months, small amt of deformed or degenerate glial elements diffusely scattered in the cerebral cortex and subcortex were observed. Clayton, G. D. and F. E. Clayton (eds.). Patty's Industrial Hygiene and Toxicology: Volume 2A, 2B, 2C: Toxicology, 3rd ed. New York: John Wiley Sons, 1981-1982., p. 4629

Fragrance Chemical	21 CFR	IID	Other
			1-Nonanol (CAS # 143-08-8) was evaluated for dermal sensitization using standard methods. The test substance was administered to 10 guinea pigs with an initial reaction rating of slight to very slight in 2 animals and a final patch rating of slight in 1 animal. The test substance was determined to be a non-sensitizer. E.I. DUPONT DE NEMOURS & CO: Primary Toxicity Tests on 15 Compounds; 12/18/47; EPA No. 86-870001072; Fiche No. OTS0514975 1-Nonanol (CAS # 142-08-8) was evaluated for primary dermal irritation. The test substance was administered to 6 New Zealand albino rabbits receiving 0.5 ml of undiluted test substance for a 24 hour exposure period. Average irritation score was 5.8/8.0. Irritation consisted of a defatting effect (skin sloughed off in 10-14 days). There was no in depth injury. 1-Nonanol (CAS # 142-08-8) was evaluated for primary eye irritation. The test substance was administered to 6 New Zealand albino rabbits receiving 0.1 ml of undiluted test substance for a 24 hour exposure period. Average irritation score was 33.3/110. Immediate discomfort was moderate with eyes tightly closed. Irritation consisted of slight erythema, copious discharge, and corneal dullness. MONSANTO CO: Initial Submission: Toxicity Studies with Nonyl Alcohol in Rats and Rabbits with Cover Letter Dated 08/13/92; 02/28/79; EPA No. 88-920007147; Fiche No. OTS0545486 Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 11. Pg. 95. 1973.
Nonyl Acetate pelargonyl acetate 143-13-5 Nonyl acetate is found in citrus peel oils, kumquat peel oil, wine grapes, apple, melon.	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Acetate C-9 was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) listed acetate C-9 (nonyl acetate), giving an	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/8918 European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2013.3169/epdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/709.pdf Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/

Fragrance Chemical	21 CFR	IID	Other
milk, beer, gruyere cheese and pepino fruits (Solanum muricaturm). NONYL ACETATE is a colorless liquid with a pungent odor of mushrooms.	ADI of 1 mg/kg. The Food Chemicals Codex (1966) has a monograph on acetate C-9.		Food and Cosmetics Toxicology. Vol. 11, Pg. 95, 1973.
Oils, styrax **Storax Oil** **Benzoin resin** styrax oil (liquidambar orientalis) essential oil of the exudate obtained from the trunk of the styrax, liquidambar orientalis, hamamelidaceae 94891-27-7 Components include: Cinnamyl Cinnamate Phenylpropyl Cinnamate Benzyl Cinnamate	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.510 - Natural flavoring substances and natural substances used in conjunction with flavors. Benzoin Resin identified as a primary component. Monograph available. A known skin sensitizer. Numerous cases of compound tincture of benzoin sensitivity have been reported in the literature, with eczema as the major dermatological manifestation (Spott & Shelley, 1970). Registry of Toxic Effects of Chemical Substances (RTECS): Benzoin https://www.cdc.gov/niosh-rtecs/DI1842F0.html	Not Listed Indicated for mild antisepsis of skin, cuts, and abrasions. No approved therapeutic indications.	PubChem not found for Styrax or Storax Oil Xi – Irritant H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation] H317 (97.15%): May cause an allergic skin reaction [Warning Sensitization, Skin] H319 (100%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] 16 Active BioAssay Results IFRA Use Restriction due to Sensitization http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl PubChem for Benzoin found https://pubchem.ncbi.nlm.nih.gov/compound/8400 MODERATELY TOXIC: PROBABLE ORAL LETHAL DOSE (HUMAN) 0.5-5.0 G/KG, BETWEEN 1 OUNCE & 1 PINT (OR 1 LB) FOR 70 KG PERSON (150 LB). Gosselin, R.E., H.C. Hodge, R.P. Smith, and M.N. Gleason. Clinical Toxicology of Commercial Products. 4th ed. Baltimore: Williams and Wilkins, 1976., p. II-156 No PK Data Levels of Evidence of Carcinogenicity: Male Rats: Negative; Female Rats: Negative; Male Mice: Negative; Female Mice: Negative. Bioassay of Benzoin for Possible Carcinogenicity (1980) Technical Rpt Series No. 204 DHEW Pub No. (NIH) 80-1760, U.S. Department of Health Education and Welfare, National Cancer Institute, Bethesda, MD 20014

Fragrance Chemical	21 CFR	IID	Other
			PERLMAN HH: Compound benzoin tincture in treatment of vesiculobullous lesions of mucous membranes. Arch Derm Syphilol. 1950 Jan:61(1):119-21. Compound tincture of benzoin: a common contact allergen? PMID 12869042: The Australasian journal of dermatology 2003 Aug:44(3):180-4 Severe allergic contact dermatitis resulting from occupational exposure to tincture of benzoin aerosol spray in an anesthesiologist. PMID 19444575: Journal of anesthesia 2009 Jan;23(2):292-4 Allergic contact dermatitis to compound tincture of benzoin. PMID 6239881: Journal of the American Academy of Dermatology 1984 Nov:11(?):847-50
Opoponax myrrh sweet 977136-06-3	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.510 - Natural flavoring substances and natural substances used in conjunction with flavors.	Not Listed	No PubChem Found No Safety or Tox data found **IFRA Use Restricted Due to Sensitization** http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl **Do not use on any part of the body because of sensitizing potential.** Use the COMMIPHORA ERYTHRAEA VAR. GLABRESCENS ENGLER type. extractives and their physically modified derivatives. it is a product which may contain resin acids and their esters, terpenes, and oxidation or polymerization products of these terpenes. (commiphora, burseraceae). http://www.thegoodscentscompany.com/data/ab1048361.html#toarte
Orris concrete (Iris pallida) orris rhizome concrete butter (iris pallida) iris pallida rhizome concrete butter 8002-73-1 977096-43-7	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.510 - Natural flavoring substances and natural substances used in conjunction with flavors. Orris concrete was given GRAS status by FEM A (1965) and orris root is approved by the FDA for food use. The Council of	Not Listed	No Pubchem Found S 24/25 - Avoid contact with skin and eyes. Food and Cosmetics Toxicology. Vol. 13, Pg. 895, 1975.

Fragrance Chemical	21 CFR	IID	Other
	Europe (1974) included orris in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The Food Chemicals Codex (1972) has a monograph on orris root.		
p-Cresol 4-hydroxytoluene 4-Methylphenol 106-44-5 **tar like odor** It is a partially lipophilic moiety which strongly binds to plasma protein (close to 100%) under normal conditions. p-Cresol is metabolized through conjugation, mainly sulphation and glucuronization. p-Cresol has been reported to affect several biochemical, biological and physiological functions: (i) it diminishes the oxygen uptake of rat cerebral cortex slices; (ii) it increases the free active drug concentration of warfarin and diazepam; (iii) it has been related to growth retardation in the weanling pig; (iv) it alters cell membrane permeability, at least in bacteria; (v) it induces LDH leakage from rat liver slices; (vi) it induces	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. 175: INDIRECT FOOD ADDITIVES: ADHESIVES AND COMPONENTS OF COATINGS § 175.300 - Resinous and polymeric coatings. **Registry of Toxic Effects of Chemical Substances (RTECS)** https://www.cdc.gov/niosh-rtecs/GO62CCF8.html **Cytotoxic to hamster ovary** **Tumorigenic to mouse skin** **Others** **EPA: Possibly carcinogenic to humans. IARC: Not evaluated. NTP: Not evaluated** **CLASSIFICATION: C; possible human carcinogen. BASIS FOR CLASSIFICATION: Based on an increased incidence of skin papillomas in mice in an initiation-promotion study. The three cresol isomers produced positive results in genetic toxicity studies both alone and in combination. HUMAN CARCINOGENICITY DATA: Inadequate. ANIMAL CARCINOGENICITY DATA: Limited.**	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/2879 **T - Toxic.** **R 24/25 - Toxic in contact with skin and if swallowed.** **R 36/37/38 - Irritating to eyes, respiratory system, and skin.** **Acute toxicity, Dermal (Category 3), H311** **H311: Toxic in contact with skin [Danger Acute toxicity, dermal]** **H314: Causes severe skin burns and eye damage [Danger Skin corrosion/irritation]** **H318: Causes serious eye damage [Danger Serious eye damage/eye irritation]** **H351: Suspected of causing cancer [Warning Carcinogenicity]** **H370: Causes damage to organs [Danger Specific target organ toxicity, single exposure]** **H372: Causes damage to organs through prolonged or repeated exposure [Danger Specific target organ toxicity, repeated exposure]** **H373: Causes damage to organs through prolonged or repeated exposure [Warning Specific target organ toxicity, repeated exposure]** **7 Active BioAssay Results** **Recommendation for para-cresol usage levels up to: 0.0500 % in the fragrance concentrate.** **INHALATION: Irritation of nose or throat. EYES: Intense irritation and pain, swelling of conjunctiva and corneal damage may occur. SKIN: Intense burning, loss of feeling, white discoloration and softening. Gangrene may occur. INGESTION: Burning sensation in mouth and esophagus. Vomiting may result. Absorption by all routes may cause muscular weakness, gastroenteric disturbance, severe depression and collapse. Effects are primarily on central**

Fragrance Chemical	21 CFR	IID	Other
susceptibility to auditive epileptic crises; and (vii) it blocks cell K+ channels. (PMID: 10570076). **p-Cresol is a uremic toxin** that is at least partially removed by peritoneal dialysis in haemodialysis patients, and has been **involved in the progression of renal failure**. (MID: 11169029). At concentrations encountered during uremia, p-cresol inhibits phagocyte function and decreases leukocyte adhesion to cytokine-stimulated endothelial cells. (PMID: 14681860). Cresols are a widely occurring natural and manufactured group of chemicals. In their pure form, they are colorless solids and may be liquids if they are mixtures. Cresols smell like medicine. There are three forms of cresols that differ slightly in their chemical structure: ortho-cresol (o-cresol), meta-cresol (m-cresol, and para-cresol (p-cresol). These forms occur separately or as a mixture. Cresols are used to dissolve other chemicals, as disinfectants and deodorizers, and to make other chemicals. Cresols may be formed normally in the body from other compounds. Cresols	**.S. Environmental Protection Agency's Integrated Risk Information System (IRIS). Summary on 4-Methylphenol (106-44-5). Available from, as of March 15, 2000:** http://www.epa.gov/iris/ **Mice were given a single dermal application of 9,10-dimethyl-1,2-benzanthracene (DMBA), a cancer initiator, followed by application of 20% solutions of o-, p-, or m-cresol in benzene twice a week for 12 weeks. This level of cresols exposure proved to be acutely toxic, producing relatively high nontumor-related mortality.** **DHHS/ATSDR: Toxicological Profile for Cresols (PB/93/110732/AS) (July 1992). Available from, as of August 7, 2006:** http://www.atsdr.cdc.gov/toxprofiles/tp34.html P-cresol is a well-known uremic toxin and environmental toxicant that may affect platelet functions. In this study, p-cresol (1-5 uM) **inhibited the arachidonic acid (AA)-induced platelet aggregation, with 47% and 82% of inhibition at concentrations of 2 and 5 uM, respectively.** These results indicate that in acute p-cresol-poisoning and long-term exposure to cresol as in severe uremic patients, p-cresol may potentially **inhibit blood clot formation and lead to hemorrhagic disorders via inhibition of platelet aggregation.** ROS production, ERK/p38 activation and TXA(2) production. Chang MC et al: Atherosclerosis 219 (2): 559-65 (2011) http://www.ncbi.nlm.nih.gov/pubmed/21993412?dopt=Abstract We predicted the safety of three biocides (p-cresol, diazinon and resmethrin) by comparing their skin permeability		**nervous system, edema of lungs, injury of spleen and pancreas may occur. (USCG, 1999)** **Toxic by all routes (ie, inhalation, ingestion, and dermal absorption)** **Effects from exposure may include nausea, contact burns to the skin and eyes, ventricular arrhythmias, pulmonary edema, seizures, coma, and death. Both the OSHA PEL and the ACGIH TLV have been set at a TWA of 5 ppm.** **Effects of Long Term Exposure** **Repeated or prolonged contact with skin may cause dermatitis. The substance may have effects on the nervous system. This may result in impaired functions. The substance may have effects on the blood. This may result in anaemia.** http://www.ilo.org/dyn/icse/showcard.display?p_version=2&p_card_id=0031 Cresols are **slightly more corrosive /to the skin or eyes/ than phenol**, but systemic effects may be a little milder because of slower absorption. Gosselin, R.E., R.P. Smith, H.C. Hodge. Clinical Toxicology of Commercial Products. 5th ed. Baltimore: Williams and Wilkins, 1984., p. II-192 p-Cresol, an end product of aromatic amino acids, is produced from food proteins by intestinal bacteria, and is detectable in blood and feces. Kawakami K et al: Immunopharmacol Immunotoxicol 31 (2): 304-9 (2009) BIOFAX Industrial Bio-Test Laboratories, Inc., Data Sheets. Vol. 5-5/1969 Journal of Pharmacology and Experimental Therapeutics. Vol. 80, Pg. 233, 1944. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2012.2573/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.1990/epdf

Fragrance Chemical	21 CFR	IID	Other
are found in many foods and in wood and tobacco smoke, crude oil, coal tar, and in chemical mixtures used as wood preservatives.	coefficients and desquamation rate (the counter flux of permeability coefficient for chemical compounds induced by skin turnover) following skin exposure. In vitro skin permeation experiments revealed that the permeability coefficients of diazinon and resmethrin were smaller than the desquamation rate; therefore, these biocides could not permeate the skin, which resulted in very low skin concentrations of these compounds. On the other hand, **the skin concentration of p-cresol was high because of its higher permeability coefficient than the desquamation rate. Furthermore, low in vitro cell viability was reported for skin exposed to p-cresol.** Sugino M et al; J Toxicol Sci 39 (3): 475-85 (2014) http://www.ncbi.nlm.nih.gov/pubmed/24849682?dopt=Abstract In an acute dermal toxicity study, technical grade ... p-cresol caused severe skin damage on at least 2/6 shaved, female, albino New Zealand rabbits within 4 hours of application of ... 300 mg/kg p-cresol. U.S. Environmental Protection Agency's Integrated Risk Information System (IRIS) on m-Cresol (108-39-4). Available from: http://www.epa.gov/iris/index.html on the Substance File List as of February 10, 2006. In rabbits that had any of the **3 cresol isomers applied dermally in doses of 1 mL/kg for 24 hr, severe edema, erythema, or subdermal hemorrhaging developed. Other effects included salivation lacrimation, hypoactivity, tremors, convulsions, sedation, and death.** Zenz, C., O.B. Dickerson, E.P. Horvath. Occupational Medicine. 3rd ed. St. Louis, MO., 1994, p. 703		http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/965.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/711.pdf Threshold Limit Value. The TLV for p-cresol has been set at 5 ppm, at which level prolonged use may cause reddening and itching of the skin and, in time, dermatitis, eczema and even ulceration. Inhalation of the vapour has caused headache, nausea and vomiting, and tremor (American Conference of Governmental Industrial Hygienists, 1970).

Fragrance Chemical	21 CFR	IID	Other
	In a study conducted on cultured rat embryos in vitro, p-cresol caused dose-related effects on growth (reduced crown-rump length, somite number and DNA content) and structural abnormalities (increased hind limb bud absence and total tail defects). WHO: Environ Health Criteria 168: Cresols (1995). Available from, as of December 22, 2014: http://www.inchem.org/pages/ehc html p-Cresol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included p-cresol in the list of artificial flavoring substances not admissible at present. Cosmetic Ingredient Review: Rated "Z": the available data are insufficient to support safety		
p-Cymene 4-methyl-1-isopropylbenzene 99-87-6 Cymene is a constituent of a number of essential oils, most commonly the oil of cumin and thyme.	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Registry of Toxic Effects of Chemical Substances (RTECS) https://www.cdc.gov/niosh-rtecs/GZ5ACA30 html European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2015.4067/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2015.4053/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2178/epdf	Not Listed	https://pubchem ncbi nlm nih.gov/compound/7463 R 20/21/22 - Harmful by inhalation, in contact with skin and if swallowed. R 36/37/38 - Irritating to eyes, respiratory system, and skin. Skin irritation (Category 2), H315 Eye irritation (Category 2A), H319 **Cosmetic Uses: masking agents** p-Cymene is reported to be a primary skin irritant ... . Monograph on Fragrance Raw Materials: p-Cymene: Food and Cosmetics Toxicology 12 (3): 401-2 (1974) p-Cymene is well absorbed through the skin. In studies with (14)C-labelled p-cymene the penetration observed was 254 ug/sq cm in 60 minutes Monograph on Fragrance Raw Materials: p-Cymene: Food and Cosmetics Toxicology 12 (3): 401-2 (1974) Food and Cosmetics Toxicology. Vol. 2. Pg. 327. 1964.

Fragrance Chemical	21 CFR	IID	Other
Pelargonium Graveolens Flower Oil **Geranium Oil** bourbon geranium flower oil Geranyl Tiglate volatile oil obtained from the flowers of the bourbon geranium, pelargonium graveolens (l.), geraniaceae 90082-51-2 8000-46-2	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.10 - Spices and other natural seasonings and flavorings. § 582.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.10 - Spices and other natural seasonings and flavorings. § 182.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). Geranium oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included geranium in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product.	Not Listed	No PubChem Found Xn - Harmful. R 36/37/38 - Irritating to eyes, respiratory system, and skin. R 43 - May cause sensitisation by skin contact. Very little Safety and Tox info available Cosmetic Uses: masking agents Irritation. Geranium oil bourbon applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973), but applied undiluted to the backs of hairless mice, it was not irritating (Urbach & Forbes, 1972). Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1973). Contact with leaves of geranium has been reported to have caused a vesicular dermatitis (Anderson, 1923). Cosmetics containing oil of geranium may cause dermatitis in hypersensitive individuals (Flandin, Rabeau & Ukrainczyk, 1937; Schwartz & Peck, 1946; Schwartz, Tulipan & Peck, 1947; Sezary & Horowitz, 1937; Tulipan, 1938).
Pentadecalactone exaltolide (Firmenich) omega-Pentadecalactone Cyclopentadecanolide Exaltolide 106-02-5 Exaltolide is found in fats and oils. Exaltolide is a constituent of angelica root oil (Angelica archangelica).	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2164/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2010.1453/epdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/975.pdf	Present in 2 approved drug products for transdermal administration at 8%.	https://pubchem.ncbi.nlm.nih.gov/compound/235414 H317 (18.4%): May cause an allergic skin reaction [Warning Sensitization, Skin] S 24/25 - Avoid contact with skin and eyes. IFRA Use Restriction due to Sensitization http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUI Food and Cosmetics Toxicology. Vol. 13, Pg. 787, 1975.
Petitgrain oil, Paraguay	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE	Not Listed	PubChem Not Found Xi - Irritant

Fragrance Chemical	21 CFR	IID	Other
citrus aurantium leaf oil paraguay 8014-17-3	§ 582.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates).		R 36/38 - Irritating to skin and eyes. R 43 - May cause sensitisation by skin contact. Skin irritation (Category 2), H315 Skin sensitisation (Category 1), H317 Eye irritation (Category 2A), H319 H315 - Causes skin irritation H317 - May cause an allergic skin reaction H319 - Causes serious eye irritation IFRA Use Restriction due to Sensitization http://www.ifraorg.org/en-us/standards-library/open/23615#.VzIgRMymqUl Food and Chemical Toxicology. Vol. 30, Pg. 101S. 1992.
Phenethyl Acetate acetic acid, 2-phenylethyl ester 103-45-7 2-Phenylethyl acetate is found in apple.	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1024/epdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/710.pdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/7654 H318 (73.73%): Causes serious eye damage [Danger Serious eye damage/eye irritation] H319 (24.64%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] Cosmetic Uses: masking agents Food and Cosmetics Toxicology. Vol. 12, Pg. 957. 1974.
Phenethyl Alcohol 2-phenylethanol 60-12-8 2-Phenylethanol is found in almond and ylang-ylang oil. Phenylethyl alcohol ... has been used in 0.5% conc as an antibacterial agent in ophthalmic solutions.	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Registry of Toxic Effects of Chemical Substances (RTECS) https://www.cdc.gov/niosh-rtecs/SG6D7B58.html Mild to Severe Eye Irritant Mutation and Reproductive Effects European Food Safety Authority (EFSA) reference(s):	Present in 10 approved products for otic, intr-articular, intramuscular, nasal and ophthalmic admin in doses ranging from 0.25 mg – 0.5% w/w.	https://pubchem.ncbi.nlm.nih.gov/compound/6054 Xn - Harmful. R 21/22 - Harmful in contact with skin and if swallowed. R 36/38 - Irritating to skin and eyes. Eye irritation (Category 2A), H319 Cosmetic Uses: masking agents 2 Active BioAssay Results Effects of Long Term Exposure Animal tests show that this substance possibly causes toxicity to human reproduction or development.

Fragrance Chemical	21 CFR	IID	Other
Grant, W.M. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986., p. 725	http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1024/epdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/930.pdf		The substance can be absorbed into the body by inhalation of its aerosol or vapour, through the skin and by ingestion. http://www.ilo.org/dyn/icse/showcard.display?p_version=2&p_card_id=0936 When instilled into the rabbit eye, 0.005 ml of undiluted material or 0.5 ml of 5 or 15% soln in propylene glycol caused severe corneal irritation and iritis ... Clayton, G. D. and F. E. Clayton (eds.). Patty's Industrial Hygiene and Toxicology: Volume 2A, 2B, 2C: Toxicology, 3rd ed. New York: John Wiley Sons, 1981-1982., p. 4642 Food and Cosmetics Toxicology. Vol. 2, Pg. 327, 1964. Toxicology and Applied Pharmacology. Vol. 28, Pg. 313, 1974.
Phenethyl Benzoate 94-47-3 Found in ceylan cinnamon.	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Phenylethyl benzoate was given GRAS status by FEM A (1965) and is approved by the FDA for food use. The Council of Europe (1974) included it at a level of 1 ppm in the list of artificial flavoring substances that may be added to foodstuffs without hazard to public health European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1024/epdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/930.pdf		https://pubchem.ncbi.nlm.nih.gov/compound/7194 Xi - Irritant R 36/38 - Irritating to skin and eyes. S 24/25 - Avoid contact with skin and eyes. 17 Active BioAssay Results Very little safety and tox information Food and Cosmetics Toxicology. Vol. 13, Pg. 905, 1975.
Phenoxyethanol **Ethylene Glycol Monophenyl Ether** 122-99-6	**175: INDIRECT FOOD ADDITIVES: ADHESIVES AND COMPONENTS OF COATINGS** **§ 175.105 - Adhesives.**	Present in 7 Drugs for topical administration (transdermal) from 0.5 – 1.05%. According to the European Union	https://pubchem.ncbi.nlm.nih.gov/compound/31236 H315 (75.94%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (72.93%): Causes serious eye irritation [Warning Serious eye damage/eye irritation]

Fragrance Chemical	21 CFR	IID	Other
It is a glycol ether used as a perfume fixative, insect repellent, antiseptic, solvent, preservative, and also as an anesthetic in fish aquaculture. phenoxyethanol acts as an effective preservative in pharmaceuticals, cosmetics and lubricants	**Listed as FLAVORING AGENT OR ADJUVANT by FDA but not included in the flavor lists** Registry of Toxic Effects of Chemical Substances (RTECS) https://www.cdc.gov/niosh-rtecs/KM55730.html Moderate to severe eye irritation Mutation Data	Cosmetics Regulation (EC) n.1223/2009, phenoxyethanol is authorized as a preservative in cosmetic formulations at a maximum concentration of 1.0%	Cosmetic Uses: preservatives 4 Active BioAssay Results Not Readily Absorbed Through The Skin In Acutely Toxic Amt. Clayton, G. D. and F. E. Clayton (eds.). Patty's Industrial Hygiene and Toxicology: Volume 2A, 2B, 2C: Toxicology. 3rd ed. New York: John Wiley Sons, 1981-1982., p. 3944 Dermal exposure to these compounds can result in localised or systemic toxicity including skin sensitisation and irritancy, reproductive, developmental and hematological effects. It has previously been shown that skin has the capacity for local metabolism of applied chemicals. Therefore, there is a requirement to consider metabolism during dermal absorption of these compounds in risk assessment for humans. Lockley DJ et al: Arch Toxicol 79 (3): 160-8 (2005) https://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel+122-99-6 Toxic by all routes (inhalation, ingestion, and dermal contact) https://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel+122-99-6 http://www.drugbank.ca/drugs/DB11304 eczema and contact urticarial reports: Bohn S and Bircher AJ: Allergy 56: 922-923 (2001) http://onlinelibrary.wiley.com/doi/10.1034/j.1398-9995.2001.00218.x/full Morton WE: Occupational phenoxyethanol neurotoxicity: a report of three cases. J Occup Med. 1990 Jan;32(1):42-5. https://www.ncbi.nlm.nih.gov/pubmed/2324842 Troutman JA, Rick DL, Stuard SB, Fisher J, Bartels MJ: Development of a physiologically-based pharmacokinetic model of 2-phenoxyethanol and its metabolite phenoxyacetic acid in rats and humans to address toxicokinetic uncertainty in risk assessment. Regul Toxicol Pharmacol. 2015 Nov;73(2):530-43. doi: 10.1016/j.yrtph.2015.07.012. Epub 2015 Jul 16. https://www.ncbi.nlm.nih.gov/pubmed/26188115 Fragrance Chemicals of Concern Present on the IFRA List 2015:

Fragrance Chemical	21 CFR	IID	Other
			https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Effects of ethylene glycol ethers on cell viability in the human neuroblastoma SH-SY5Y cell line. Pharmacol Rep. 2010 Nov-Dec;62(6):1243-9. It has been found that 2-phenoxyethanol in a concentration-dependent manner (5-25 mM, 24 h) increased the basal and H(2)O(2)-induced lactate dehydrogenase (LDH) release and 3-[4,5-dimethylthiazol-2-yl]2,5-diphenyl tetrazolium bromide (MTT) reduction. 2-phenoxyethanol showed the most consistent cytotoxic effect on neurons in in vitro conditions and enhanced the hydrogen peroxide action It is concluded that the results of the present study should be confirmed in in vivo conditions and that some EGEs, especially 2-phenoxyethanol, 2-butoxyethanol and 2-isopropoxyethanol, may be responsible for initiation or exacerbation of neuronal cell damage. The relative toxicity of compounds used as preservatives in vaccines and biologics. Med Sci Monit. 2010 May;16(5):SR21-7. https://www.ncbi.nlm.nih.gov/pubmed/20424565 In vitro induction of apoptosis vs. necrosis by widely used preservatives: 2-phenoxyethanol, a mixture of isothiazolinones, imidazolidinyl urea and 1,2-pentanediol. Biochem Pharmacol. 2002 Feb 1;63(3):437-53. https://www.ncbi.nlm.nih.gov/pubmed/11853695 2-Phenoxyethanol: a neurotoxicant? Arch Toxicol. 2000 Jul;74(4-5):281-7. https://www.ncbi.nlm.nih.gov/pubmed/10959804 Journal of Industrial Hygiene and Toxicology. Vol. 23, Pg. 259, 1941. Union Carbide Data Sheet. Vol. 6/24/1958 Journal of the American College of Toxicology. Vol. 9, Pg. 259, 1990. Food Chem Toxicol. 2012 Sep;50 Suppl 2:S244-55

Fragrance Chemical	21 CFR	IID	Other
Phenylacetaldehyde 122-78-1 Found in some essential oils, e.g. Citrus spp., Tagetes minuta (Mexican marigold) and in the mushroom Phallus impudicus (common stinkhorn)	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1024/epdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/930.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/710.pdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/998 H314 (74.67%): Causes severe skin burns and eye damage [Danger Skin corrosion/irritation] H317 (96.46%): May cause an allergic skin reaction [Warning Sensitization, Skin] H318 (71.51%): Causes serious eye damage [Danger Serious eye damage/eye irritation] R 43 - May cause sensitisation by skin contact. Skin irritation (Category 2). H315 Eye irritation (Category 2A). H319 4 Active BioAssay Results IFRA Use Restriction due to Sensitization http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 17, Pg. 377, 1979. Toksikologicheskii Vestnik. Vol. (2), Pg. 35, 1995.
p-Methyl Acetophenone 4'-Methylacetophenone 122-00-9 Present in sour cherry, orange, grapefruit peel, blackcurrants, guava, peach, other fruits, celery, potato, tomato, pepper, parsley, smoked fish, cognac, Parmesan cheese and other foodstuffs.	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. p-Methylacetophenone was granted GRAS status by FEM A (1965) and is approved by the FDA for food use. The Council of Europe (1970) listed p-methylacetophenone giving an ADI of 1 mg/kg. The Food Chemicals Codex (1972) has a monograph on p-methylacetophenone. European Food Safety Authority (EFSA) reference(s):	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/8500 H315 (79.94%): Causes skin irritation [Warning Skin corrosion/irritation] R 36/38 - Irritating to skin and eyes. Cosmetic Uses: masking agents Irritation. p-Methylacetophenone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Calandra, 1971). Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/

Fragrance Chemical	21 CFR	IID	Other
	http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2016.4557/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1022/epdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/869.pdf		Food and Cosmetics Toxicology. Vol. 12, Pg. 933, 1974.
Pogostemon Cablin Oil Patchouli Oil Patchouly, Oil (Pogostemon Spp.) 8014-09-3 Volatile oil obtained from the leaves of the patchouli, pogostemon cablin, labiatae Patchoulol or patchouli alcohol is the major component.	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.510 - Natural flavoring substances and natural substances used in conjunction with flavors.	Not Found	PubChem Not Found Xi – Irritant R 36/38 - Irritating to skin and eyes. Skin corrosion/irritation (Category 3), H316 H316 - Causes mild skin irritation A pharmacokinetic study of patchouli alcohol after a single oral administration of patchouli alcohol or patchouli oil in rats. Eur J Drug Metab Pharmacokinet. 2016 Aug;41(4):441-8 the pharmacokinetics profile was linear in both the patchouli alcohol and patchouli oil groups. The C max and AUC0-t of patchouli alcohol were greater in all three doses of patchouli alcohol compared to corresponding patchouli oil doses. Additionally, the T max values were significantly greater in the patchouli oil group. These results suggest that the other ingredients in patchouli oil influence the pharmacokinetic behavior of patchouli alcohol during its absorption. Patchouli alcohol, an essential oil of Pogostemon cablin, exhibits anti-tumorigenic activity in human colorectal cancer cells. Int Immunopharmacol. 2013 Jun;16(2):184-90. These findings suggest that PA exerts an anti-cancer activity by decreasing cell growth and increasing apoptosis in human colorectal cancer cells. The proposed mechanisms include the inhibition of HDAC2 expression and HDAC enzyme activity, and subsequent downregulation of c-myc and activation of NF-κB pathway. Food and Chemical Toxicology. Vol. 20, Pg. 791, 1982.
Propanedioic acid, diethyl ester Diethyl Malonate 105-53-3	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants.	Not Found	https://pubchem.ncbi.nlm.nih.gov/compound/7761 Xi – Irritant H319 (100%): Causes serious eye irritation [Warning Serious eye damage/eye irritation]

Fragrance Chemical	21 CFR	IID	Other
Diethyl malonate is present in guava fruit, melon, concord grape, pineapple, blackberry and many wines and spirits.	**Registry of Toxic Effects of Chemical Substances (RTECS)** https://www.cdc.gov/niosh-rtecs/OOAAE60.html **Skin Irritant** **Tumorigenic: Active as anti-cancer agent** European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2164/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2010.1453/epdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/975.pdf Diethyl malonate was given GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1974) included it in the list of artificial flavoring substances that may be added temporarily to foodstuffs without hazard to public health. The Food Chemicals Codex (1972) has a monograph on diethyl malonate.		R 36 - Irritating to eyes. 1 Active BioAssay Result Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was very slightly irritating (Moreno, 1975). Smyth et al. (1969) also reported only very slight irritation of rabbit skin after application of undiluted diethyl malonate, but application of 0-005 ml of undiluted diethyl malonate to the rabbit cornea caused severe burning. Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ American Industrial Hygiene Association Journal. Vol. 30, Pg. 470, 1969.
Propanoic acid, phenylmethyl ester benzyl propionate 122-63-4 Benzyl propionate is found in muskmelon.	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Benzyl propionate was given GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1974) listed benzyl propionate, giving an ADI of 5 mg/kg. The Food Chemicals Codex (1972) has a monograph on benzyl propionate.	Not Found	https://pubchem.ncbi.nlm.nih.gov/compound/31219 Irritation. Benzyl propionate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was irritating (Moreno, 1973). Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology, Vol. 13, Pg. 723, 1975.

Fragrance Chemical	21 CFR	IID	Other
	European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2176/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1025/epdf		
Santalum Album (Sandalwood) Oil 8006-87-9 977020-85-1	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.510 - Natural flavoring substances and natural substances used in conjunction with flavors. Sandalwood oil was granted GRAS status by FEMA (1965). The Council of Europe (1970) included sandalwood in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The Food Chemicals Codex (1972) has a monograph on sandalwood oil.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/16072318 Xi – Irritant R 36/38 - Irritating to skin and eyes. R 43 - May cause sensitisation by skin contact. Skin irritation (Category 2), H315 Skin sensitisation (Category 1), H317 Eye irritation (Category 2A), H319 Cosmetic Uses: skin conditioning Irritation. Undiluted sandalwood oil EI applied to the backs of hairless mice was slightly irritating (Urbach & Forbes, 1972), and applied full strength to intact or abraded rabbit skin for 24 hr under occlusion it was irritating (Shelanski, 1971). A Anticancer Effects of Sandalwood (Santalum album). Anticancer Res. 2015 Jun;35(6):3137-45. A rare type of sesquiterpene and β-santalol derivatives from Santalum album and their cytotoxic activities. Chem Pharm Bull (Tokyo). 2014;62(12):1192-9. cis-β-Santalol (9) and β-santaldiol (10) induced apoptotic cell death in HL-60 cells. α-Santalol derivatives from Santalum album and their cytotoxic activities. Phytochemistry. 2012 May;77:304-11. Fragrance contact dermatitis in Korea: a joint study. Contact Dermatitis. 2005 Dec;53(6):320-3. Sandalwood oil (Santalum album L.) showed high frequencies of positive responses. Food Chem Toxicol. 2008 Feb;46(2):421-32.

Fragrance Chemical	21 CFR	IID	Other
Tanacetum vulgare, ext. Tansy Extract of the herb, flowers and seeds of the tansy, tanacetum vulgare l., compositae 84961-64-8 8016-87-3	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.510 - Natural flavoring substances and natural substances used in conjunction with flavors. Many tansy species contain a volatile oil which can cause contact dermatitis in sensitive individuals. If taken internally, toxic metabolites are produced as the oil is broken down in the liver and digestive tract. **Because it contains thujone, the U.S. FDA limits the use of tansy to alcoholic beverages, and the final product must be thujone-free.** Tansy was formerly used as a flavoring for puddings and omelets, but is now almost unknown. The Council of Europe (1974) included tansy oil in the list of currently used flavouring substances for which the toxicological and technological data are deemed insufficient; their use is temporarily admitted possibly with a limitation on the active principle in the final product. **Tansy oil, like other essential oils containing large amounts of thujone, is a poison which causes convulsions and epileptic-like attacks (Tucakov, 1960).**	Not Listed	No PubChem Found Irritation. Undiluted tansy oil was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1974), but was slightly irritating when applied to intact or abraded rabbit skin for 24 hr under occlusion (Moreno, 1974). Skin. In studies on the intact shaved abdominal skin of mice, percutaneous absorption of tansy oil was rapid (38 min) (Meyer & Meyer, 1959). A severe case of eczematous dermatitis caused by T. vulgare plants, including a similar reaction to ingestion of an extract intended for desensitization, was reported by Greenhouse & Sulzberger (1933). Medicinal and veterinary use. The essential oil of Tanacetum is a vermifuge (because of its thujone content), emmenagogue and **abortifacient** (Tucakov, 1960).
Tartaric Acid 526-83-0 It occurs naturally in many plants, particularly grapes, bananas, and tamarinds, is	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.1099 - Tartaric acid. § 582.6099 - Tartaric acid. 310: NEW DRUGS § 310.545 - Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.	Present in 31 Approved Drug products for IM, IV, Oral, Sucutaneous, Topical administration	https://pubchem.ncbi.nlm.nih.gov/compound/875 H315 (54.25%): Causes skin irritation [Warning Skin corrosion/irritation] H317 (39.85%): May cause an allergic skin reaction [Warning Sensitization, Skin] H318 (40.09%): Causes serious eye damage [Danger Serious eye damage/eye irritation]

Fragrance Chemical	21 CFR	IID	Other
commonly combined with baking soda to function as a leavening agent in recipes, and is one of the main acids found in wine. It is added to other foods to give a sour taste and is used as an antioxidant. Salts of tartaric acid are known as tartrates.	331: ANTACID PRODUCTS FOR OVER-THE-COUNTER (OTC) HUMAN USE § 331.11 - Listing of specific active ingredients. 341: COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTIASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE § 341.3 - Definitions. 184: DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE § 184.1099 - Tartaric acid. not for fragrance use.		Not for fragrance use.
Terpineol mixture of p-methenols 8000-41-7 Reported to be found in more than 200 derivatives from leaves, herbs and flowers [Fenarolfs Handbook of Flavor Ingredients, 1971 ; Gildemeister & Hoffman, 1962).	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Terpineol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. It was listed by the Council of Europe (1970) with an ADI of 1 mg/kg, and is the subject of a Food Chemicals Codex (1972) monograph. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2015.4118/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2010.1336/epdf	Alpha Terpineol is approved in one drug product for topical administration at 11%.	https://pubchem.ncbi.nlm.nih.gov/compound/17100 H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (77.79%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] Xi - Irritant R 36/38 - Irritating to skin and eyes. Dermal Systemic Exposure in Cosmetic Products: 0.0744 mg/kg/day (IFRA, 2003) 5 Active BioAssay Results Cosmetic Uses: denaturants masking agents perfuming agents solvents As judged by pine oil, terpineols are irritating to eyes and mucous membranes. Produce hemorrhagic gastritis when ingested. Gosselin, R.E., R.P. Smith, H.C. Hodge, Clinical Toxicology of Commercial Products, 5th ed. Baltimore: Williams and Wilkins, 1984., p. II-260

Fragrance Chemical	21 CFR	IID	Other
			Two dermatitis patients were reported to be sensitized to alpha-terpineol, although attempts to induce skin sensitization in volunteers using a dilute solution of alpha-terpineol were unsuccessful. BIBRA Working Group: TA: Toxicity Profile. TNO BIBRA Intl (2001) https://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel+98-55-5 **After iv injection of 0.1 mL/kg, death due to massive pulmonary edema occurred within minutes.** In this animal blood and tissue levels of alpha-terpineol of between 150 and 300 ppm were observed. After smaller doses of pine oil (0.033 mL/kg), horses survived until euthanized up to 48 hr later. Blood levels of alpha-terpineol became undetectable in one of these animals after 2 hr, and no tissue levels were detected at postmortem.... Tobin T et al: Res Commun Chem Pathol Pharm 15 (2): 291 (1976) http://www.ncbi.nlm.nih.gov/pubmed/981787?dopt=Abstract Irritation. Terpineol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1971). Percutaneous absorption. Terpineol was rapidly absorbed through the intact shaved abdominal skin of the mouse (Meyer & Meyer, 1959). Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
Thymus Vulgaris (Thyme) Oil 8007-46-3 85085-75-2 Essential oil obtained from the herbs of the thyme, thymus zygis l., lamiaceae	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates).	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/6850745 R 34 - Causes burns. S 24/25 - Avoid contact with skin and eyes. Irritation. Undiluted thyme oil, red applied to the backs of hairless mice was **severely irritating** (Urbach & Forbes, 1973). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it **was again severely irritating** (Moreno, 1973).

Fragrance Chemical	21 CFR	IID	Other
	Thyme oil was granted GRAS status by FEM A (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included thyme oil in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. The Food Chemicals Codex (1972) has a monograph on thyme oil.		Alternative treatment of vaginal infections – in vitro antimicrobial and toxic effects of Coriandrum sativum L. and Thymus vulgaris L. essential oils. J Appl Microbiol. 2015 Sep;119(3):697-710. Thyme EO showed slightly better fungicidal activity reaching MIC at 0·11 mg ml(-1) for all C. albicans strains. Thymus vulgaris essential oil: chemical composition and antimicrobial activity. J Med Life. 2014;7 Spec No. 3:56-60. Cytotoxicity of Thymus vulgaris essential oil towards human oral cavity squamous cell carcinoma. Anticancer Res. 2011 Jan;31(1):81-7. Food and Cosmetics Toxicology. Vol. 12, Pg. 1003, 1974. Pharmazie. Vol. 11, Pg. 628, 1956.
Undecan-2-one nonyl methyl ketone **Methyl nonyl ketone** 112-12-9 2-Undecanone is found in cloves, palm kernel oil and soya bean oil, black currant buds, raspberry, black berry peach and other fruits.	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2015.4268/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2012.2495/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1020/epdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/8163 S 24/25 - Avoid contact with skin and eyes. 7 Active BioAssay Results In an eye irritation study, methyl nonyl ketone was observed to **cause conjunctival irritation in 6/6 New Zealand white rabbits through 24 hours**, 4/6 at 48 hours, 2/6 at 72 hours, 1/6 at 4 days and 0/6 at 7 days. In a dermal irritation study in New Zealand white rabbits, erythema and eschar formation were present in 6/6 animals through 72 hours and 3/6 at 7 days; edema was noted in 5/6 at 30-60 minutes, 2/6 at 24-72 hours and 0/6 at 7 days. USEPA/Office of Pesticide Programs: Reregistration Eligibility Decision Document - Methyl nonyl ketone. EPA 738-R-95-038 July 1995. Available from, as of February 23, 2006: http://www.epa.gov/pesticides/reregistration/status.htm Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Acta Pharmaceutica Jugoslavica. Vol. 12, Pg. 79, 1962. Food and Cosmetics Toxicology. Vol. 13, Pg. 869, 1975.

Fragrance Chemical	21 CFR	IID	Other
Undecylenal 10-undecenal (aldehyde C-11 undecylenic) 10-undecenal 112-45-8 10-Undecenal is found in herbs and spices such as coriander leaf (Coriandrum sativum).	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Aldehyde C11, undecylenic was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1972) included aldehyde C-11, undecylenic in the list of admissible artificial flavoring substances at a level of **0.2 ppm**. The Food Chemicals Codex (1972) has a monograph on aldehyde C-11, undecylenic. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2016.4559/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2010.1400/epdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/616.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/204.pdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/8187 H315 (99.9%): Causes skin irritation [Warning Skin corrosion/irritation] H317 (91%): May cause an allergic skin reaction [Warning Sensitization, Skin] H319 (93.39%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] R 36/38 - Irritating to skin and eyes. R 43 - May cause sensitisation by skin contact. Acute toxicity, dermal (Category 5), H313 Skin irritation (Category 2), H315 Skin sensitisation (Category 1), H317 Eye irritation (Category 2A), H319 Serious eye damage/eye irritation (Category 2A), H320 1 Active BioAssay Result (Androgen Receptor) Cosmetic Uses: masking agents perfuming agents Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 11, Pg. 479, 1973.
Vanillin benzaldehyde, 4-hydroxy-3-methoxy- 121-33-5 Vanillin is the primary component of the extract of the vanilla bean. Synthetic vanillin, instead of natural vanilla extract, is sometimes used as a flavoring agent in foods.	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.60 - Synthetic flavoring substances and adjuvants. 172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.60 - Synthetic flavoring substances and adjuvants.	Present in 26 drug products for oral administration in doses ranging up 65.5 mg. MeSH Pharmacological Classification: Antimutagenic Agents Antioxidants Anticonvulsants	https://pubchem.ncbi.nlm.nih.gov/compound/1183#section=Top H320: Causes eye irritation [Warning Serious eye damage/eye irritation] Eye irritation (Category 2A), H319 10 Active BioAssay Results Cosmetic Uses: masking agents Highly irritating action on the eyes and mucous membranes of the respiratory tract. Lewis, R.J. Sax's Dangerous Properties of Industrial Materials, 9th ed. Volumes 1-3. New York, NY: Van Nostrand Reinhold, 1996., p. 84

Fragrance Chemical	21 CFR	IID	Other
beverages, and pharmaceuticals.	§ 182.90 - Substances migrating to food from paper and paperboard products. 135: FROZEN DESSERTS § 135.110 - Ice cream and frozen custard. 169: FOOD DRESSINGS AND FLAVORINGS § 169.180 - Vanilla-vanillin extract. § 169.181 - Vanilla-vanillin flavoring. § 169.182 - Vanilla-vanillin powder. Vanillin was given GRAS status by FEMA (1965) and is approved by the FDA for food use(GRAS). The Council of Europe (1974) listed vanillin, giving it an ADI of 10 mg/kg. Both the Food Chemicals Codex (1972) and the United States Pharmacopeia (1975) have monographs on vanillin and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for vanillin, giving an unconditional ADI of 0-10 mg/kg. **Registry of Toxic Effects of Chemical Substances (RTECS)** https://www.cdc.gov/niosh-rtecs/YW581E98.html **Reproductive Effects to Ovaries, fallopian tubes, Uterus, cervix, vagina following subcutaneous administration to rats (20 mg/kg 4D prior to copulation)** European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2013.EN-440/pdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2176/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1025/epdf		Irritation. In closed-patch tests on human skin, vanillin caused no primary irritation when tested at concentrations of 20% on 29 normal subjects, of 2% on 30 normal subjects and of 0-4% in 35 subjects with dermatoses (Fujii, Furukawa & Suzuki, 1972). Sensitization. Maximization tests (Kligman, 1966; Kligman & Epstein, 1975) were carried out on groups of 25 volunteers. The material was tested at concentrations of 2% (Greif, 1967) and 5% (Kligman, 1970) in petrolatum and produced no sensitization reactions. Positive reactions to vanillin were reported in eight out of 142 patients who were already sensitized to balsam of Peru (Mitchell, 1975). In studies of sensitization to balsam of Peru and its components (Hjorth, 1961), vanillin (pure or 10% in vaseline) produced positive patch-test reactions in 21 out of 164 patients sensitive to the balsam. Vanillin was considered to be a secondary allergen, since sensitivity was found only in patients sensitive to vanilla, isoeugenol and coniferyl benzoate. Cross sensitization to other substituted benzaldehydes was particularly uncommon. Vanillin was found not to be responsible for most cases of sensitivity to natural vanilla. Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 2, Pg. 327, 1964. Journal of the American Pharmaceutical Association, Scientific Edition. Vol. 29, Pg. 425, 1940. National Technical Information Service. Vol. OTS0533712

Fragrance Chemical	21 CFR	IID	Other
Vetiveria Zizanoides Root Oil Vetiver Oil 8016-96-4 977059-70-3 The main constituents of vetiver oil are vetiverol and vetiverone {Fenarolfs Handbook of Flavor Ingredients. 1971 ; Guenther. 1950). 68129-81-7	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.510 - Natural flavoring substances and natural substances used in conjunction with flavors. Vetiver oil is approved by the FDA for food use. The Council of Europe (1970) included vétiver oil in the list of flavouring substances temporarily admitted for use, possibly with a limitation on the active principle in the final product.	Not Listed	PubChem Not Found for Root Oil or Vetiver Oil. PubChem found for vetiverol and vetiverone: https://pubchem.ncbi.nlm.nih.gov/compound/101549 https://pubchem.ncbi.nlm.nih.gov/compound/85904#section=Top Irritation. Undiluted vétiver oil applied to the backs of hairless mice was not irritating (Urbach & Forbes, 1973). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, the oil was moderately irritating (Moreno, 1973). Vetiverol: H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation] H317 (99.53%): May cause an allergic skin reaction [Warning Sensitization, Skin] H319 (100%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] Cosmetic Uses: masking agents perfuming agents tonic Vetiverol is listed on: Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 12, Pg. 1013, 1974.

APPENDIX B: SHOWER TO SHOWER FRAGRANCE CHEMICAL REVIEW

Fragrance Chemical	21 CFR	IID	Other
1-Benzazole	Present in Baby Powder Product. Refer to Table above.		
1-Cedr-8-en-9-ylethanone	Present in Baby Powder Product. Refer to Table above.		
1-Methoxy-4-methylbenzene P-Methyl anisole p-CRESYL METHYL ETHER p-methoxytoluene 104-93-8 3494-45-9 1-Methoxy-4-methylbenzene is found in garden tomato. 1-Methoxy-4-methylbenzene is isolated from ylang-ylang, cananga and other essential oils. Also present in tomato and Camembert cheese.	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. 182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.60 - Synthetic flavoring substances and adjuvants. 582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.60 - Synthetic flavoring substances and adjuvants. p-Cresyl methyl ether was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) included p-cresyl methyl ether in the list of admissible artificial flavoring substances at a level of 5 ppm. The Food Chemicals Codex (1972) has a monograph on p-cresyl methyl ether. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2012.2678/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2158/epdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/833.pdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/7731#section=Canonical-SMILES **Xn - Harmful.** **R 38 - Irritating to skin.** **Skin irritation (Category 2), H315** **Reproductive toxicity (Category 2), H361** **H315 - Causes skin irritation** **H361 - Suspected of damaging fertility or the unborn child** **H319: Causes serious eye irritation** p-Cresyl methyl ether applied full strength on intact or abraded rabbit skin was moderately irritating (Hart, 1971). 2 Active BioAssay Results Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 12, Pg. 393, 1974.

Fragrance Chemical	21 CFR	IID	Other
2,6-Dimethylheptan-2-ol Freesia Heptanol Dimetol (Givaudan) Freesiol Lolitol 13254-34-7 Not found in nature.	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2010.1336/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.1847/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2015.4118/epdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/83268 **Xi - Irritant** **R 36/38 - Irritating to skin and eyes** **H315: Causes skin irritation** **H319: Causes serious eye irritation** Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Fragrance material review on 2,6-dimethyl-2-heptanol. Food Chem Toxicol. 2010 Jul;48 Suppl 4:S110-4. doi: 10.1016/j fct.2010.05.041. https://www.ncbi.nlm.nih.gov/pubmed/20659632 Food and Chemical Toxicology. Vol. 30, Pg. 23S, 1992.
2-Acetonaphthone	Present in Baby Powder Product. Refer to Table above.		
2-Nonanone, 3-(hydroxymethyl)- **3-(Hydroxymethyl)nonan-2-one** 2-Acetyl-1-octanol herbal ketone methyl lavender ketone (IFF) 67801-33-6	Could Not Locate in 21 CFR Could not locate FDA UNII Could not locate EFSA references No IFRA Standard	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/106823#section=Canonical-SMILES **H315 (100%): Causes skin irritation** **H319 (100%): Causes serious eye irritation** Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
2-Octanol, 2,6-dimethyl **Tetrahydromyrcenol** 18479-57-7 Not Found in Nature	Could Not Locate in 21 CFR Could not locate FDA UNII Could not locate EFSA references	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/86751 **Xi - Irritant** **R 36/38 - Irritating to skin and eyes** **Serious eye damage/eye irritation (Category 2A), H320** **H320 - Causes eye irritation** not for flavor use. maximum skin levels for fine fragrances: 0.7100 % and are based on the assumption that the fragrance mixture is used at 20% in a consumer product (IFRA Use Level Survey). (IFRA, 2004)

Fragrance Chemical	21 CFR	IID	Other
			Dermal Systemic Exposure in Cosmetic Products: 0.064 mg/kg/day (IFRA, 2004) Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
2-Propanol, 1,1'-oxybis-	Present in Baby Powder Product. Refer to Table above.		
2-t-Butylcyclohexyl Acetate cis-green acetate 20298-69-5 88-41-5 Not Found In Nature	Could Not Locate in 21 CFR UNII: 87JN7005XU Could not locate EFSA references No IFRA Standard	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/62334 Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
3,7-Dimethylnona-2,6-dienenitrile **Homogeranyl Nitrile** Lemonile 3,7-Dimethyl-2,6-nonadienenitrile 61792-11-8 Not Found In Nature	Could Not Locate in 21 CFR Could not locate FDA UNII Could not locate EFSA references No IFRA Standard	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/112446 Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Chemical Toxicology. Vol. 30, Pg. 27S. 1992.
3,7-Dimethyloct-6-en-1-ol	Present in Baby Powder Product. Refer to Table above.		
3,7-Dimethylocta-2,6-dien-1-ol Geraniol	Present in Baby Powder Product. Refer to Table above.		
3-Cyclohexene-1-carboxaldehyde, 3-(4-hydroxy-4-methylpentyl)- 3,4-leerall LYRALDEHYDE 51414-25-6	Could Not Locate in 21 CFR Could not locate FDA UNII Could not locate EFSA references	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/162105 **H317 (100%): May cause an allergic skin reaction [Warning Sensitization, Skin]** **IFRA Critical Effect: Sensitization** http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl

Fragrance Chemical	21 CFR	IID	Other
31906-04-4			limits in the finished product for - "leave on the skin contact": 1.5000 % Restriction. Category 5 Restriction 0.2% Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
3-Methylbutyl salicylate isoamyl salicylate 87-20-7 Isoamyl salicylate is found in alcoholic beverages, is isolated from fruit aromas. Also present in rum and black tea.	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. Amyl salicylate was granted GRAS status by FEM A (1965) and is approved by the FDA for food use. The Council of Europe (1970) included amyl salicylate (isoamyl salicylate) in the list of admissible artificial flavouring substances at a level of 3 ppm. The Food Chemicals Codex (1972) has a monograph on amyl salicylate. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2176/epdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/637.pdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/6874 **Xi N - Irritant, Dangerous for the environment.** **R 36/37 - Irritating to eyes and respiratory system.** **Skin corrosion/irritation (Category 3), H316** **H316 - Causes mild skin irritation** Dermal Systemic Exposure in Cosmetic Products: 0.1042 mg/kg/day (IFRA. 2002) Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Toksikologicheskii Vestnik. Vol. (2). Pg. 25. 1994. Fragrance material review on isoamyl salicylate. Food Chem Toxicol. 2007:45 Suppl 1:S418-23. Epub 2007 Sep 14.
3-Octanol, 3,7-dimethyl- Tetrahydrolinalool linalool tetrahydride 78-69-3 57706-88-4	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants European Food Safety Authority (EFSA) reference(s):	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/6548 **H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation]** **H319 (99.8%): Causes serious eye irritation [Warning Serious eye damage/eye irritation]** **Xi - Irritant** **R 36/38 - Irritating to skin and eyes.** **Skin irritation (Category 2), H315** **Eye irritation (Category 2A), H319**

Fragrance Chemical	21 CFR	IID	Other
Found in grapefruit juice, lemongrass, mango, orange juice.	http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/978.pdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/331.pdf		Dermal Systemic Exposure in Cosmetic Products: 0.0005 mg/kg/day Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 17, Pg. 909, 1979.
4,7-Methano-IH-indenol, 3a,4,5,6,7,7a-hexahydro-, propanoate **Dicyclopentadiene Propionate** Tricyclodecenyl Propionate Verdyl propionate 68912-13-0 not found in nature	Could Not Locate in 21 CFR Could not locate FDA UNII Could not locate EFSA references No IFRA Standard	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/3034895 **Skin corrosion/irritation Cat 3** **H316: Causes mild skin irritation** Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
Acetic acid, anhydride, reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene amber decatriene trimofix O (IFF) 1-(2,5,10-Trimethylcyclododeca-2,5,9-trien-1-yl)ethanone Ketone, methyl 2,5,10-trimehtyl-2,5,9-cyclododecatrien-1-yl 144020-22-4	Could Not Locate in 21 CFR Could not locate FDA UNII Could not locate EFSA references	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/53422908 **H317 (97.13%): May cause an allergic skin reaction [Warning Sensitization, Skin]** **Xi - Irritant** **R 36/37/38 - Irritating to eyes, respiratory system, and skin.** **IFRA Critical Effect: Dermal sensitization** http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl Category 5: 1.31 % Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/

Fragrance Chemical	21 CFR	IID	Other
1391529-52-4 Not Found In Nature			Evaluation of the developmental toxicity of 4-tert-butylcyclohexyl acetate in Sprague-Dawley rats. PMID 23064702: International journal of toxicology 2012 Jan:31(5):477-82
Acetic acid, p-tert-butylcyclohexyl ester woody acetate (4-tert-butylcyclohexyl) acetate 4-tert-Butylcyclohexyl acetate 1900-69-2 10411-92-4 32210-23-4 Not Found In Nature	Could Not Locate in 21 CFR FDA UNII ATR4EHD017 Could not locate EFSA references No IFRA Standard	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/4-tert-Butylcyclohexyl_acetate **Xi - Irritant** **R 36 - Irritating to eyes.** **Skin irritation (Category 2), H315** **Eye irritation (Category 2A), H319** Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 16, Pg. 657, 1978.
Aloe Barbadensis Leaf Extract ALOE, EXTRACT (ALOE SPP.) 94349-62-9 84837-08-1 8001-97-6 **Not a fragrance** **No IFRA Standard**	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.510 - Natural flavoring substances and natural substances used in conjunction with flavors. European Food Safety Authority (EFSA) reference(s): Safety of hydroxyanthracene derivatives for use in food: http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2018.5090/epdf	Not Listed	No PubChem cosmetic and flavor agents, dietary supplements not for fragrance use. Cosmetic Usage: emollients humectants oral care agents skin conditioning Indian Journal of Experimental Biology. Vol. 6, Pg. 232, 1968. Int J Toxicol. 2007;26 Suppl 2:1-50. Final report on the safety assessment of AloeAndongensis Extract, Aloe Andongensis Leaf Juice,aloe Arborescens Leaf Extract, Aloe Arborescens Leaf Juice, Aloe Arborescens Leaf Protoplasts, Aloe Barbadensis Flower Extract, Aloe Barbadensis Leaf, Aloe Barbadensis Leaf Extract, Aloe Barbadensis Leaf Juice,aloe Barbadensis Leaf Polysaccharides, Aloe Barbadensis Leaf Water, Aloe Ferox Leaf Extract, Aloe Ferox Leaf Juice, and Aloe Ferox Leaf Juice Extract. https://www.ncbi.nlm.nih.gov/pubmed/17613130 "Aloe barbadensis (also known as Aloe vera)-derived ingredients were not toxic in acute oral studies using mice and rats."

Fragrance Chemical	21 CFR	IID	Other
			"Aloe barbadensis extracted with water and given to pregnant Charles Foster albino rats on gestational days (GDs) 0 through 9 was an abortifacient and produced skeletal abnormalities. Both negative and positive results were found in bacterial and mammalian cell genotoxicity assays using Aloe barbadensis-derived material, Aloe Ferox-derived material, and various anthraquinones derived from Aloe." "Other animal data also suggest that components of Aloe inhibit tumor growth and improve survival." "Case reports include acute eczema, contact urticaria, and dermatitis in individuals who applied Aloe-derived ingredients topically. The Cosmetic Ingredient Review Expert Panel concluded that anthraquinone levels in the several Aloe Barbadensis extracts are well understood and can conform to the industry-established level of 50 ppm. Although the phototoxicity anthraquinone components of Aloe plants have been demonstrated, several clinical studies of preparations derived from Aloe barbadensis plants demonstrated no phototoxicity, confirming that the concentrations of anthraquinones in such preparations are too low to induce phototoxicity."
Amyl Cinnamal	Present in Baby Powder Product. Refer to Table above.		
Amyris Balsamifera Bark Oil **AMYRIS, OIL (AMYRIS BALSAMIFERA L.)** volatile oil distilled from the bark of the tree, amyris balsamifera, rutaceae 8015-65-4	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.510 - Natural flavoring substances and natural substances used in conjunction with flavors. Amyris oil is approved by the FDA for food use. The Council of Europe (1970) included amyris oil (Amyris balsamifera) in the list of temporarily admitted flavouring substances. The Food Chemicals Codex (1972) has a monograph on amyris oil.	Not Listed	No PubChem **H315 Causes skin irritation.** **H319 Causes serious eye irritation** **Skin Irrit. 2 - H315;** **Eye Irrit. 2 - H319** Food and Cosmetics Toxicology. Vol. 2, Pg. 327. 1964.
Anthemis Nobilis Flower Oil **CHAMAEMELUM NOBILE FLOWER OIL**	182: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 182.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates).	Not Listed	No PubChem **Xi - Irritant** **R 38 - Irritating to skin.**

Fragrance Chemical	21 CFR	IID	Other
CHAMOMILE FLOWER, OIL (ANTHEMIS NOBILIS L.) volatile oil distilled from the dried flower heads of the roman chamomile, anthemis nobilis l., asteraceae 8015-92-7	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.20 - Essential oils, oleoresins (solvent-free), and natural extractives (including distillates).		Food and Cosmetics Toxicology. Vol. 12, Pg. 853, 1974.
Benzophenone Diphenylketone 119-61-9 852361-03-6 Benzophenone is found in fruits. Benzophenone is present in grapes. FDA also is amending the food additive regulations to no longer provide for the use of benzophenone as a flavor in foods. https://www.federalregister.gov/documents/2018/10/09/2018-21807/food-additive-regulations-synthetic-flavoring-agents-and-adjuvants	~~172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION~~ ~~§ 172.515 - Synthetic flavoring substances and adjuvants.~~ ~~FDA PART 177 - INDIRECT FOOD ADDITIVES: POLYMERS~~ ~~Subpart C - Substances for Use Only as Components of Articles Intended for Repeated Use~~ ~~Sec. 177.2600 Rubber articles intended for repeated use.~~ 701: COSMETIC LABELING § 701.3 - Designation of ingredients. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2017.5013/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1104/epdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/869.pdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/3102 **Xi N - Irritant, Dangerous for the environment.** **R 36/37/38 - Irritating to eyes, respiratory system, and skin.** **Carcinogenicity (Category 2), H351** **H351 - Suspected of causing cancer** **H373 (34.95%): Causes damage to organs through prolonged or repeated exposure [Warning Specific target organ toxicity, repeated exposure]** **15 Active BioAssay Results** Cosmetic Uses: masking agents uv absorbers Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 11, Pg. 873, 1973. European Journal of Toxicology and Environmental Hygiene. Vol. 9, Pg. 99, 1976. Toxicological evaluation of benzophenone http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1104/epdf Natl Toxicol Program Tech Rep Ser. 2006 Feb;(533):1-264.

Fragrance Chemical	21 CFR	IID	Other
	Benzophenone was granted GRAS status by FEM A (1965) and ~~is approved by the FDA for food use~~. The Council of Europe (1970) included benzophenone in the list of admissible artificial flavoring substances at a level of 2 ppm. The Food Chemicals Codex (1972) has a monograph on benzophenone. **Registry of Toxic Effects of Chemical Substances (RTECS)** https://www.cdc.gov/niosh-rtecs/DI97D330.html **No IFRA Standard**		Toxicology and carcinogenesis studies of benzophenone (CAS No. 119-61-9) in F344/N rats and B6C3F1 mice (feed studies). "Under the conditions of these 2-year studies, there was some evidence of carcinogenic activity of benzophenone in male F344/N rats based on increased incidences of renal tubule adenoma; mononuclear cell leukemia in male F344/N rats may have been related to benzophenone exposure. There was equivocal evidence of carcinogenic activity of benzophenone in female F344/N rats based on the marginally increased incidences of mononuclear cell leukemia and histiocytic sarcoma. There was some evidence of carcinogenic activity of benzophenone in male B6C3F1 mice based on increased incidences of hepatocellular neoplasms, primarily adenoma. There was some evidence of carcinogenic activity of benzophenone in female B6C3F1 mice based on increased incidences of histiocytic sarcoma; the incidences of hepatocellular adenoma in female B6C3F1 mice may have been related to benzophenone exposure. Administration of benzophenone in feed resulted in increased incidences and/or severities of nonneoplastic lesions in the kidney and liver of male and female rats and in the liver, kidney, nose, and spleen of male and female mice. Decreased incidences of mammary gland fibroadenoma in female rats were related to benzophenone exposure." Toxic Rep Ser. 2000 Apr;(61):1-53, A1-13. NTP technical report on the toxicity studies of benzophenone (CAS No. 119-61-9). Administered in feed to F344/N rats and B6C3F mice. "The kidney was also identified as a target organ of benzophenone toxicity in rats only, based on exposure concentration-related increases in kidney weights and microscopic changes. The no-observed-adverse-effect level for benzophenone was not achieved in these studies." Food Chem Toxicol. 1991 Nov;29(11):741-50. Safety evaluation of benzophenone. "A no-effect level was demonstrated at 20 mg/kg/day for 90 days of administration. This would be equivalent to an intake of 1200 mg/day for a 60-kg human. On the basis of the calculated Possible Average Daily Intake of 0.33 mg/day, a safety factor of greater than 3600 is demonstrated. The safety factor based on the more realistic per capita consumption of 0.32 microgram/day would be approximately 3.7 million."

Fragrance Chemical	21 CFR	IID	Other
			J Urol. 2007 Oct;178(4 Pt 2):1637-42. Epub 2007 Aug 16. In utero exposure to benzophenone-2 causes hypospadias through an estrogen receptor dependent mechanism. "These findings suggest that benzophenone-2 may cause hypospadias via signaling through the estrogen receptor. Further study of human benzophenone-2 exposure and its effects is needed to support this hypothesis." Food Chem Toxicol. 2007 May;45(5):843-51. Epub 2006 Nov 15. Carcinogenesis studies of benzophenone in rats and mice. "There was some evidence of carcinogenic activity of benzophenone in male B6C3F(1) mice based on increased incidences of hepatocellular neoplasms, primarily adenoma. There was some evidence of carcinogenic activity of benzophenone in female B6C3F(1) mice based on increased incidences of histiocytic sarcoma; the incidences of hepatocellular adenoma in female B6C3F(1) mice may have been related to benzophenone exposure."
Benzyl Benzoate	Present in Baby Powder Product.		Refer to Table above.
Benzyl Salicylate	Present in Baby Powder Product.		Refer to Table above.
Cinnamyl Alcohol	Present in Baby Powder Product.		Refer to Table above.
Citronellyl Nitrile 3,7-dimethyloct-6-enenitrile 51566-62-2 Not found in nature	Could Not Locate in 21 CFR Could not locate FDA UNII Could not locate EFSA references Could not locate FEMA monograph No IFRA Standard	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/3033030 **Xi - Irritant** **R 36/38 - Irritating to skin and eyes.** **H319 (92.6%): Causes serious eye irritation [Warning Serious eye damage/eye irritation]** **H331 - Toxic if inhaled** **Acute toxicity, Oral (Category 4), H302** **Acute toxicity, inhalation (Category 3), H331** Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 17, Pg. 525, 1979. Food Chem Toxicol. 2001 Feb;39(2):147-51.

Fragrance Chemical	21 CFR	IID	Other
			An assessment of the release of inorganic cyanide from the fragrance materials benzyl cyanide, geranyl nitrile and citronellyl nitrile applied dermally to the rat. https://www.ncbi.nlm.nih.gov/pubmed/11267708 "Organonitriles are widely used as components of fragrances that are incorporated into consumer products, many of which are for human topical use. Some organontriles are readily broken down metabolically to potentially toxic inorganic cyanide. Studies were therefore undertaken to assess whether this occurs with three representative fragrance nitriles, namely, benzyl cyanide, geranyl nitrile and citronellyl nitrile when applied dermally to the rat." "For geranyl nitrile there was no significant increase in urinary thiocyanate excretion and there was only a marginal increase in the case of citronellyl nitrile that was equivalent to 0.40% of the applied dose for males and 0.29% for females." Drug Metab Dispos. 2006 Jun;34(6):1019-29. Epub 2006 Mar 15. Comparative metabolism of geranyl nitrile and citronellyl nitrile in mouse, rat, and human hepatocytes. https://www.ncbi.nlm.nih.gov/pubmed/16540590 "Geranyl nitrile (GN) and citronellyl nitrile (CN) are fragrance components used in consumer and personal care products. Differences in the clastogenicity of these two terpenes are postulated to result from differential biotransformation, presumably involving the conjugated nitrile moiety. The metabolic clearance and biotransformation of GN and CN were compared in primary hepatocytes from mice, rats, and humans." "Thus, the presumed metabolic basis for differences in genotoxicity remains elusive." Food Chem Toxicol. 2013 Sep;59:784-92. doi: 10.1016/j.fct.2013.04.040. Epub 2013 Apr 30. Evaluation of genotoxicity of nitrile fragrance ingredients using in vitro and in vivo assays. https://www.ncbi.nlm.nih.gov/pubmed/23643699 "Genotoxicity studies were conducted on a group of 8 fragrance ingredients that belong to the nitrile family. These nitriles are widely used in consumer products however there is very limited data in the literature regarding the genotoxicity of these nitriles. The 8 nitriles were assessed for genotoxicity using an Ames test, in vitro chromosome aberration test or in vitro micronucleus test. The positive results observed in the in vitro tests were further investigated using an in vivo micronucleus test. The results from

Fragrance Chemical	21 CFR	IID	Other
			these different tests were compared and these 8 nitriles are not considered to be genotoxic." "While citronellyl nitrile, 3-methyl-5-phenylpentanenitrile, cinnamyl nitrile, and 3-methyl-5-phenylpent-2-enenitrile revealed positive results in the in vitro tests, but confirmatory in vivo tests determined these nitriles to be negative in the in vivo micronucleus assay."
Commiphora Myrrha Oil myrrh oil 8016-37-3 Prepared by steam distillation of crude myrrh, an essential oil is obtained, appropriately called Myrrh Oil. Includes pinene, dipentene, & limonene. tsca definition 2008: extractives and their physically modified derivatives. commiphora, burseraceae.	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.510 - Natural flavoring substances and natural substances used in conjunction with flavors. Myrrh oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1974) included myrrh oil in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. The Food Chemicals Codex (1972) has a monograph on myrrh oil.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/substance/349327141#section=Top https://pubchem.ncbi.nlm.nih.gov/substance/135326586 **Xn - Harmful.** **R 22 - Harmful if swallowed.** **R 36/38 - Irritating to skin and eyes.** **Skin irritation (Category 2), H315** **Skin sensitisation (Category 1), H317** **Serious eye damage/eye irritation (Category 2A), H320** **H317 - May cause an allergic skin reaction** Food and Cosmetics Toxicology. Vol. 14. Pg. 621. 1976. Fitoterapia. 2004 Jan:75(1):81-4. Irritant potential of some constituents from oleo-gum-resin of Commiphora myrrha. https://www.ncbi.nlm.nih.gov/pubmed/14693226
Coumarin	Present in Baby Powder Product. Refer to Table above.		
Cyclamen Aldehyde	Present in Baby Powder Product. Refer to Table above.		
Diethyl Phthalate 84-66-2 68988-18-1 Diethyl phthalate is classified as a member of the benzoic acid esters. Diethyl phthalic acid is considered to be practically insoluble (in water)	175: INDIRECT FOOD ADDITIVES: ADHESIVES AND COMPONENTS OF COATINGS § 175.105 - Adhesives. § 175.300 - Resinous and polymeric coatings. § 175.320 - Resinous and polymeric coatings for polyolefin films.	Listed in 12 products (capsules and tablets) for oral administration up to 20.5 mg per dose.	https://pubchem.ncbi.nlm.nih.gov/compound/6781 **Xn - Harmful.** **R 36/37/38 - Irritating to eyes, respiratory system, and skin.** **H315 (22.62%): Causes skin irritation [Warning Skin corrosion/irritation]** **H319 (50%): Causes serious eye irritation [Warning Serious eye damage/eye irritation]** **H331 (28.57%): Toxic if inhaled [Danger Acute toxicity, inhalation]**

Fragrance Chemical	21 CFR	IID	Other
and basic. This substance is commonly used to make plastics more flexible. **Phthalate esters can cause reproductive and developmental toxicity.** Not found in nature **Diethyl Phthalate is not a fragrance.** **No IFRA Standard**	176: INDIRECT FOOD ADDITIVES: PAPER AND PAPERBOARD COMPONENTS § 176.170 - Components of paper and paperboard in contact with aqueous and fatty foods. 177: INDIRECT FOOD ADDITIVES: POLYMERS § 177.1200 - Cellophane. § 177.2600 - Rubber articles intended for repeated use. 178: INDIRECT FOOD ADDITIVES: ADJUVANTS, PRODUCTION AIDS, AND SANITIZERS § 178.2010 - Antioxidants and/or stabilizers for polymers. § 178.3910 - Surface lubricants used in the manufacture of metallic articles. 181: PRIOR-SANCTIONED FOOD INGREDIENTS § 181.27 - Plasticizers. Approved for indirect food contact, approved in 12 oral drugs. Does not appear to be approved for topical use. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2004.1062/epdf **Registry of Toxic Effects of Chemical Substances (RTECS):** https://www.cdc.gov/niosh-rtecs/TI100590.html **Reproductive Effects and Tumorigenic**		**H373 (11.9%): Causes damage to organs through prolonged or repeated exposure [Warning Specific target organ toxicity, repeated exposure]** Cosmetic Uses: denaturants film formers hair conditioning masking agents plasticisers solvents **Not for fragrance use.** **12 Active BioAssay Results** Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Absorption, Distribution and Excretion: International Programme on Chemical Safety (IPCS); Concise International Chemical Assessment Document (CICADS) 52: Diethyl Phthalate (2003) Available from, as of April 17, 2008: http://www.inchem.org/documents/cicads/cicads/cicad52.htm "Absorption of diethyl phthalate and three other phthalates (dimethyl, dibutyl, and di(2-ethylhexyl)) was measured using human epidermal skin obtained from the abdominal skin of 11 cadavers (mostly females 55 years of age or older) and subcutaneous fat removed in vitro. Epidermal membranes were set up in glass diffusion cells, and their permeability to tritiated water was measured to establish the integrity of the skin. Lag time for absorption of diethyl phthalate was 6 hr, and the steady-state absorption rate was 12.8 ug/sq cm per hour." "Male rats exposed to a single dermal application of (14)C-diethyl phthalate (5-8 mg/sq cm) excreted 24% of the administered dose in the urine and 1% of the dose in feces within 24 hr." Linked to abnormal development of reproductive organs in baby boys and sperm damage in adult men (Washington Toxics Coalition 2009).

Fragrance Chemical	21 CFR	IID	Other
			Links prenatal exposure of DEP to clinically diagnosed Attention Deficit Disorder in children (Engel 2010). In a study of 130 Danish and Finish infants, scientists noted an association between the levels of DEP metabolite in the mother's breast milk and alterations in levels of male sex hormones in the baby boys (Main 2006). A recent study in Mexico associated high levels of urinary DEP and an elevated risk of breast cancer (Lopez-Carrillo 2010). Infants' phthalate levels correlated with their mothers' reported use of baby lotion, powder and shampoo (Sathyanarayaya 2008). **Evaluating the potential genotoxicity of phthalates esters (PAEs) in perfumes using in vitro assays** **ENVIRONMENTAL SCIENCE AND POLLUTION RESEARCH** **Volume: 24 Issue: 30 Pages: 23903-23914** **DOI: 10.1007/s11356-017-9978-1** https://link-springer-com.ezproxy.lib.utexas.edu/content/pdf/10.1007%2Fs11356-017-9978-1.pdf Journal of Pharmaceutical Sciences. Vol. 61, Pg. 51, 1972. "Industrial Hygiene and Toxicology," 2nd ed., Patty, F.A., ed., New York, John Wiley & Sons, Inc., 1958-63Vol. 2, Pg. 1904, 1963.
Dihydrocitronellol dimethyl octanol 3,7-dimethyl-1-octanol Tetrahydrogeraniol 106-21-8 1333-49-9 68680-98-8 1117-60-8	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. 3,7-Dimethyl-1-octanol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1970) listed 3,7-dimethyl-1-octanol (tetrahydrogeraniol), giving an ADI of 5	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/7792 **H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation]** **H319 (97.37%): Causes serious eye irritation [Warning Serious eye damage/eye irritation]** **Xi N - Irritant, Dangerous for the environment.** **R 36/38 - Irritating to skin and eyes.** **Skin irritation (Category 2), H315** **Eye irritation (Category 2A), H319**

Fragrance Chemical	21 CFR	IID	Other
59204-02-3 Present in lemon oil and thyme.	mg/kg. The Food Chemicals Codex (1972) has a monograph on 3,7-dimethyl-1-octanol. European Food Safety Authority (EFSA) reference(s): http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/709.pdf		**Specific target organ toxicity - single exposure (Category 3), Respiratory system, H335** **Dermal Systemic Exposure in Cosmetic Products: 0.0005 mg/kg/day** **6 Active BioAssay tests** Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ 3,7-Dimethyl-1-octanol applied full strength on intact or abraded rabbit skin produced irritation (Shelanski & Moldovan, 1973b). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1973). J Control Release. 1998 Nov 13;55(2-3):297-302. Penetration enhancing effect of tetrahydrogeraniol on the percutaneous absorption of 5-fluorouracil from gels in excised rat skin. "Poly(acrylic acid) gels containing 5-fluorouracil (5-FU) and tetrahydrogeraniol (THG) were prepared and the effects of THG on 5-FU permeation across the excised rat skin were studied by in vitro methods. Experiments on in vitro permeation of 5-FU across the skin with vertical diffusion cells showed that addition of THG to the gels markedly enhanced the 5-FU permeability." Food Chem Toxicol. 2008 Nov;46 Suppl 11:S139-41. doi: 10.1016/j.fct.2008.06.023. Epub 2008 Jul 1. Fragrance material review on 3,7-dimethyl-1-octanol. Food and Cosmetics Toxicology. Vol. 12, Pg. 535, 1974.
Eugenol 4-Allyl-2-methoxyphenol 4-allylguaiacol; 97-53-0	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. 184: DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE	Present in an oral elixir. Potency per dose is not disclosed.	https://pubchem.ncbi.nlm.nih.gov/compound/3314 **H317 (99.88%): May cause an allergic skin reaction [Warning Sensitization, Skin]** **H319 (94.97%): Causes serious eye irritation [Warning Serious eye damage/eye irritation]** **R 42/43 - May cause sensitization by inhalation and skin contact.** **Skin sensitisation (Category 1), H317**

Fragrance Chemical	21 CFR	IID	Other
Eugenol is a cinnamate derivative of the shikamate pathway found in CLOVE OIL and other PLANTS. Eugenol is the main constituent of several important essential oils such as oil of clove, clove stem and leaf, pimenta berry and leaf, bay and cinnamon leaf. Eugenol is a **Standardized Chemical Allergen**. The physiologic effect of eugenol is by means of Increased Histamine Release, and Cell-mediated Immunity. There are a number of unapproved OTC products that advertise it for the use of toothache. Eugenol is is also commonly used in combination with zinc oxide in dental procedures for the cementation of temporary prostheses and the temporary restoration of teeth and cavities.	§ 184.1257 - Clove and its derivatives. 310: NEW DRUGS § 310.545 - Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses. 582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.60 - Synthetic flavoring substances and adjuvants. 872: DENTAL DEVICES § 872.3275 - Dental cement. Eugenol was granted GRAS status by FEMA (1965) and is approved by the FDA as GRAS for food use. The Council of Europe (1974) included eugenol in the list of artificial flavoring substances that may be added to foodstuffs without hazard to public health, giving an ADI of 5 mg/kg. The Food Chemicals Codex (1972) and the United States Pharmacopeia (1965) both have monographs on eugenol. The Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for eugenol giving a conditional ADI of 0-5 mg/kg. Evaluations of the Joint FAO/WHO Expert Committee on Food Additives - JECFA: adjusted ADI to 0-2.5 mg/kg bw (1982 and reaffirmed in 2005). http://whqlibdoc.who.int/trs/WHO_TRS_934_eng.pdf European Food Safety Authority (EFSA) reference(s): https://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2440/epdf		**Eye irritation (Category 2A), H319** **14 Active BioAssay Results** **IFRA Critical Effect: Sensitization** http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl **Category 5: 0.50 %** **This compound is a primary irritant and sensitizer and can cause contact dermatitis. Irritation of the skin, eyes and respiratory tract occurs. Ingestion of this compound may cause gastroenteritis, vomiting and gastric secretion of mucin.** **Skin contact may cause an inflammatory reaction on the skin. Prolonged or repeated skin contact may cause allergic dermatitis. Eye contact may cause burns. Skin sensitization may also occur. Symptoms of exposure to this type of compound include intense irritation of all tissues, circulatory collapse, dysuria, hematuria, unconsciousness, tachycardia, pulmonary edema, bronchial pneumonia, abortion and irreversible renal damage.** Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ The stomachs of rats and guinea-pigs given oral doses of 150mg eugenol/animal showed histological damage consisting of desquamation of the epithelium and punctate haemorrhages in the pyloric and glandular regions (Hartiala, Pulkkinen & Ball, 1966). In tests on acute toxicity to mucous membranes, eugenol applied bilaterally to the ventral surface of the tongue of dogs for 5 min caused erythema and occasionally ulcers with a moderate diffuse inflammatory infiltration (Lilly, Cutcher & Jendresen, 1972). Eugenol tested at 8% in petrolatum produced a mild irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1971). A patch test using undiluted eugenol for 24 hr produced no reactions in 20 subjects (Katz, 1946).

Fragrance Chemical	21 CFR	IID	Other
	http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/965.pdf		No penetration of mouse skin was demonstrated after dermal application of eugenol. IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Geneva: World Health Organization. International Agency for Research on Cancer. 1972-PRESENT. (Multivolume work). Available at: http://monographs.iarc fr/ENG/Classification/index.php . p. V36 86 (1985) Patch tests for eugenol in patients suffering from 'cosmetic dermatitis' were positive in 2.6% (4/155) of cases. IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Geneva: World Health Organization. International Agency for Research on Cancer. 1972-PRESENT. (Multivolume work). Available at: http://monographs.iarc fr/ENG/Classification/index.php . p. V36 87 (1985) During a five-year period 3,065 patients with contact dermatitis were patch tested using a specific mix of fragrances. 509 (16.6%) patients were allergic to the fragrance mix, while 258 (8.4%) patients exhibited an allergic reaction to Myroxylon pereirae (balsam of Peru). Between those 509 patients, 157 were patch tested with eight individual substances contained in the fragrance mix: cinnamal, cinnamyl alcohol, eugenol, isoeugenol, geraniol, hydroxycitronellal, alpha-amyl cinnamal and Evernia prunastri (oak moss). The most frequent allergens were isoeugenol 57.9% (91/157), eugenol 55.4% (87/157), cinnamyl alcohol 34.4% (54/157) and Evernia prunastri (oak moss) 24.2% (38/157). Turic P et al; Coll Antropol. 2011 Mar:35(1):83-7 (2011) http://www ncbi nlm nih gov/pubmed/21661358?dopt=Abstract Natl Toxicol Program Tech Rep Ser. 1983 Dec:223:1-159. Carcinogenesis Studies of Eugenol (CAS No. 97-53-0) in F344/N Rats and B6C3F1 Mice (Feed Studies). "For mice there was equivocal evidence of carcinogenicity since eugenol caused increased incidences of both carcinomas and adenomas of the liver in male mice at the 3,000 ppm dietary level and because eugenol was associated with an increase in the combined incidences of hepatocellular carcinomas or adenomas in female mice. Levels of Evidence of Carcinogenicity: Male Rats: Negative Female Rats: Negative Male Mice: Equivocal Female Mice: Equivocal Synonym"

Fragrance Chemical	21 CFR	IID	Other
			https://www.ncbi.nlm.nih.gov/pubmed/12778213 Food and Cosmetics Toxicology. Vol. 2. Pg. 327. 1964. Archives of Toxicology. Vol. 59. Pg. 78. 1986.
Geraniol	Present in Baby Powder Product. Refer to Table above.		
Hexamethylindanopyran	Present in Baby Powder Product. Refer to Table above.		
Hexane. 1-methoxy- methyl hexyl ether diola (IFF) 4747-07-3	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2013.3092/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2158/epdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/78484 **Xi – Irritant** **R 38 - Irritating to skin.** Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/
Indisan (Sandela) reaction product Could not locate	Could not locate		
Isoeugenol 2-methoxy-4-(1-methylvinyl)phenol 97-54-1 5932-68-3 Isoeugenol is a commonly used fragrance added to many commercially available products. and occurs naturally in the essential oils of plants such as ylang-ylang. It is also a **significant dermatologic sensitizer and allergen**. and as a result has been restricted to	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR *HUMAN CONSUMPTION* § 172.515 - Synthetic flavoring substances and adjuvants. Isoeugenol was given GRAS status by FEMA (1965) and is approved by the FDA for food use. The Council of Europe (1974) listed isoeugenol. giving an ADI of 5 mg/kg. The Food Chemicals Codex (1972) has a monograph on isoeugenol. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2012.2532/epdf	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/853433 **H312 (96.11%): Harmful in contact with skin [Warning Acute toxicity, dermal]** **H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation]** **H317 (99.73%): May cause an allergic skin reaction [Warning Sensitization, Skin]** **H319 (99.82%): Causes serious eye irritation [Warning Serious eye damage/eye irritation]** **R 36/37/38 - Irritating to eyes, respiratory system, and skin.** **R 43 - May cause sensitisation by skin contact.** **Skin irritation (Category 2), H315** ***Skin sensitisation (Category 1), H317*** **Eye irritation (Category 2A), H319** **IFRA Critical Effect: Sensitization** http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl

Fragrance Chemical	21 CFR	IID	Other
200 p.p.m. since 1998 according to guidelines issued by the fragrance industry [A34278]. Sensitivity to Isoeugenol may be identified with a clinical patch test.	http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.1991/epdf		**Category 5: 0.02 %** **6 Active BioAssay results** Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Isoeugenol tested at 8% in petrolatum produced a mild irritation after a 48-hr closed patch test on human subjects (Kligman, 1971). In closed-patch tests on human skin, isoeugenol in Vaseline or ointment caused primary irritation (erythema) in three of 35 normal subjects and in one of 30 normal subjects when applied in concentrations of 5 and 2%, respectively, while erythema resulted in one of 54 subjects with dermatoses tested with a concentration of 0*1% in 99% ethanol or a cream base (Fujii, Furukawa & Suzuki, 1972). Moderate skin reactions in guinea-pigs resulted when 1% isoeugenol in peanut oil was applied to the injection site 3 wk after a 10-day course of daily intradermal injections of a 0.1%, suspension of isoeugenol (Griepentrog, 1961). Thompson GR et al; Food Chem Toxicol 21 (6): 735-40 (1983) Andersen KE et al; Toxicol Appl Pharmacol 170 (3): 166-71 (2001) Turic P et al; Coll Antropol. 2011 Mar;35(1):83-7 (2011)
Isopropyl Palmitate isopropyl hexadecanoate propan-2-yl hexadecanoate 142-91-6 Isopropyl palmitate is a fatty acid ester obtained by the formal condensation of carboxy group of palmitic acid with propan-2-ol. Metabolite	Not listed for food use. 310: NEW DRUGS § 310.545 - Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses. "Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses. A number of active ingredients have been present in OTC drug products for various uses, as described below. However, based on evidence currently available, there are inadequate data	Present in 14 drug products for topical and transdermal administration.	https://pubchem.ncbi.nlm.nih.gov/compound/8907#section=Top Cosmetic Uses: Not a fragrance antistatic agents binding agents emollients perfuming agents skin conditioning solvents **H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation]**

Fragrance Chemical	21 CFR	IID	Other
observed in cancer metabolism. It has a role as a human metabolite.	to establish general recognition of the safety and effectiveness of these ingredients for the specified uses: isopropyl palmitate is included in skin protectant drug products." European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2017.4725/epdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/722.pdf **Registry of Toxic Effects of Chemical Substances (RTECS)** https://www.cdc.gov/niosh-rtecs/RT4AC4A0.html **No IFRA Standard**		**H319 (66.67%): Causes serious eye irritation [Warning Serious eye damage/eye irritation]** **1 Active BioAssay results** Effects of isopropyl palmitate on the skin permeation of drugs. Biol Pharm Bull. 2006 Nov;29(11):2324-6. https://www.ncbi.nlm.nih.gov/pubmed/17077540 Food and Chemical Toxicology. Vol. 20, Pg. 727, 1982.
Levisticum Officinale Oil levisticum officinale root oil LOVAGE OIL 8016-31-7 Essential oil obtained from the roots of the lovage, levisticum officinale, apiaceae	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.510 - Natural flavoring substances and natural substances used in conjunction with flavors.	Not Listed	No PubChem **Xi - Irritant** **R 36/38 - Irritating to skin and eyes.** Food and Cosmetics Toxicology. Vol. 16, Pg. 813, 1978.
Methyl Benzoate	Present in Baby Powder Product. Refer to Table above.		
Methyl Hydrogenated Rosinate	Present in Baby Powder Product. Refer to Table above.		
Musk Ketone 4-tert-butyl-2,6-dimethyl-3,5-dinitroacetophenone 81-14-1	Not listed in CFR *The Council of Europe (1974) included musk ketone in the list of artificial flavoring substances that may be added temporarily to foodstuffs without hazard to public health.*	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/6669 **H351 (99.74%): Suspected of causing cancer [Warning Carcinogenicity]** **9 Active BioAssay results** Fragrance Chemicals of Concern Present on the IFRA List 2015:

Fragrance Chemical	21 CFR	IID	Other
	OPINION OF THE SCIENTIFIC COMMITTEE ON COSMETIC PRODUCTS AND NON-FOOD PRODUCTS INTENDED FOR CONSUMER Evaluation and opinion on Musk xylene and Musk ketone http://ec.europa.eu/health/ph_risk/committees/sccp/documents/out280_en.pdf SCIENTIFIC COMMITTEE ON HEALTH AND ENVIRONMENTAL RISKS (SCHER) Opinion on Classification of Musk ketone http://ec.europa.eu/health/ph_risk/committees/04_scher/docs/scher_o_022.pdf **"classify musk ketone as "category 3 carcinogen" based on read across."**		https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ IFRA fragrance material specification: Musk ketone should only be used if it contains less than 0.1% of musk xylene. http://www.ifraorg.org/en-us/standards-library/open/23615#.VzJgRMvmqUl HSDB https://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel+81-14-1 HUMAN STUDIES: Musk ketone failed to elicit a sensitization reaction after 48 and 72 hours in a maximization test with human volunteers. A case described patient with chronic actinic dermatitis whose photopatch tests revealed reactions to musk ketone and musk ambrette, both of which were found in his aftershave lotion. Musk ketone at doses of 0.068 to 68 uM did not induce sister chromatid exchanges in human lymphocytes with or without metabolic activation. In an in vitro micronucleus test, musk ketone at doses up to 136 and 250 uM did not increase the frequency of micronuclei in human lymphocytes and in the human hepatoma cell line Hep G2, respectively. ANIMAL STUDIES: Musk ketone did not produce dermal irritation or systemic toxicity in rabbits. It was a mild eye irritant in rabbit's eyes. Musk ketone did not produce contact sensitivity in guinea pigs. Musk ketone treatment in mice resulted in dose-related increases in relative liver weight at dose levels of 50 mg/kg bw, up to 50% at 500 mg/kg bw. Musk ketone also caused histological changes in the liver, primarily centrilobular hepatocellular hypertrophy, and at the highest dose panlobular hepatocellular hypertrophy. Pregnant rats received by gavage 0, 60, 200, 600 or 2,000 mg musk ketone/kg bw/day during days 7-17 of gestation. Observations after caesarean sectioning showed decreases in fetal body weights, litter sizes and live fetuses and increases in early and late resorptions and percent resorbed conceptuses at 200 mg/kg bw and higher. No gross external fetal alterations were observed. Musk ketone negatively affects reproduction and early life-stage survival in zebrafish. Musk ketone was tested in 5 strains of Salmonella typhimurium and found to be negative with and without activation. Food Chem Toxicol. 1990 Jan;28(1):55-61.

Fragrance Chemical	21 CFR	IID	Other
			90-day dermal toxicity study and neurotoxicity evaluation of nitromusks in the albino rat. https://www.ncbi.nlm.nih.gov/pubmed/2312014 Food Chem Toxicol. 1996 Jul;34(7):633-8. An evaluation of genotoxicity tests with Musk ketone. Musk ketone did not show genotoxic potential based on the negative results in the mouse lymphoma, in vitro cytogenetics and in vitro UDS assays Toxicol Lett. 1999 Dec 20;111(1-2):169-74. Developmental toxicity studies of four fragrances in rats. "Developmental toxicity occurred at the high-dosages of … musk ketone (increased postimplantation loss and reduced fetal body weight at 150 mg/kg per day). The results of this study indicate that under conditions of normal use, the tested fragrances do not pose a risk to human conceptuses." Int J Hyg Environ Health. 2001 May;203(4):293-9. Evaluation of health risks caused by musk ketone. "Several studies provided convincing evidence of lack of a genotoxic potential for MK. However, MK was identified as a strong inducer of phase I enzymes in rodents and a cogenotoxicant in vitro in human derived cells in rather low doses, suggesting that exposure to MK might increase the susceptibility to health hazards caused by carcinogens in humans." Mutat Res. 2001 Aug 22;495(1-2):89-96. Musk ketone enhances benzo(a)pyrene induced mutagenicity in human derived Hep G2 cells. "The results of the present study show that MK amplifies the genotoxic effects of B(a)P in human derived cells and indicate that exposure of humans to MK might increase their susceptibility to the health hazards of B(a)P and other polycyclic aromatic hydrocarbons." Food and Cosmetics Toxicology. Vol. 13, Pg. 877, 1975.
Myristica Fragrans (Nutmeg) Kernel Oil	Present in Baby Powder Product. Refer to Table above.		
Octan-2-one 2-octanone methyl hexyl ketone	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/8093#section=Top **Xn - Harmful.** **R 21 - Harmful in contact with skin.**

Fragrance Chemical	21 CFR	IID	Other
111-13-7 2-Octanone is a trace constituent of plant oils, apple, apricot, banana, papaya, wheat bread, other breads, cheddar cheese, Swiss cheese, coffee, black tea, roasted filbert, plum brandy and cooked shrimp.	§ 172.515 - Synthetic flavoring substances and adjuvants. Methyl hexyl ketone was given GRAS status by FEM A (1965) and is approved by the FDA for food use. The Council of Europe (1974) included methyl hexyl ketone at a level of 2 ppm in the list of artificial flavoring substances that may be added to foodstuffs without hazard to public health. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2015.4268/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1020/epdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/164.pdf		**R 36/37/38 - Irritating to eyes, respiratory system, and skin.** **1 Active BioAssay Result** Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ 2-Octanone has a relatively low toxicity. Direct skin contact may cause defatting and irritation of the skin. Inhalation may produce mild symptoms of eye, nose, and throat irritation at low concentrations, and may cause /CNS depression/ at high concentrations. Produced slight irritation when applied undiluted to rabbit eyes 2-Octanone applied to the skin of guinea pigs produced slight to moderate skin irritation. Guinea pigs lost weight during a 2-week period following occluded application to the skin, suggesting that 2-octanone may have been absorbed percutaneously. Bingham, E.; Colrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons, New York, N.Y. (2001)., p. 6:301 Toxicology Letters, Vol. 30, Pg. 13, 1986.
Phenethyl Alcohol	Present in Baby Powder Product. Refer to Table above.		
Pogostemon Cablin Oil Patchouli Oil PATCHOULY, OIL (POGOSTEMON SPP.) Volatile oil obtained from the leaves of the patchouli, pogostemon cablin, labiatae 8014-09-3	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.510 - Natural flavoring substances and natural substances used in conjunction with flavors.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/substance/135316842#section=Top **Xi - Irritant** **R 36/38 - Irritating to skin and eyes.** **Aspiration hazard (Category 1), H304** **Skin corrosion/irritation (Category 3), H316** Food and Chemical Toxicology, Vol. 20, Pg. 791, 1982.
Propanoic acid, phenylmethyl ester Benzyl Propionate Phenylmethyl Propionate	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.515 - Synthetic flavoring substances and adjuvants.	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/31219 S 24/25 - Avoid contact with skin and eyes. Fragrance Chemicals of Concern Present on the IFRA List 2015:

Fragrance Chemical	21 CFR	IID	Other
122-63-4	Benzyl propionate was given GRAS status by FEM A (1965) and is approved by the FDA for food use. The Council of Europe (1974) listed benzyl propionate, giving an ADI of 5 mg/kg. The Food Chemicals Codex (1972) has a monograph on benzyl propionate. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2176/epdf http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1025/epdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/637.pdf		https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Benzyl propionate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973). Fragrance material review on benzyl propionate. PMID 22414642: Food Chem Toxicol. 2012 Sep:50 Suppl 2:S486-90 RIFM fragrance ingredient safety assessment, Benzyl propionate, CAS Registry Number 122-63-4. Food Chem Toxicol. 2016 Nov:97S:S38-S48 Food and Cosmetics Toxicology. Vol. 13, Pg. 723, 1975.
Propylene Glycol DL-1.2-propanediol 57-55-6 Propylene glycol is a clear, colorless, viscous organic solvent and diluent used in pharmaceutical preparations. **Propylene Glycol is not a fragrance.**	169: FOOD DRESSINGS AND FLAVORINGS § 169.175 - Vanilla extract. 172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.850 - Lactylated fatty acid esters of glycerol and propylene glycol. 184: DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE § 184.1666 - Propylene glycol. 349: OPHTHALMIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE § 349.12 - Ophthalmic demulcents. 350: ANTIPERSPIRANT DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE § 350.10 - Antiperspirant active ingredients.	Present in 184 drug products for buccal, topical, transdermal, oral otic, intramuscular, intravenous, ophthalmic, rectal, vaginal administration.	https://pubchem.ncbi.nlm.nih.gov/compound/1030 **H302 (14.16%): Harmful if swallowed [Warning Acute toxicity, oral]** **H319 (49.56%): Causes serious eye irritation [Warning Serious eye damage/eye irritation]** **1 Active BioAssay result** **Irritation-Eyes, Nose, Throat, Skin—Mild (HE16) from OSHA Chemical Sampling Information** **Source: OSHA Chemical Sampling Information** **Record Name: Propylene glycol:** https://www.osha.gov/dts/chemicalsampling/data/CH_264480.html Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Cosmetic Uses: humectants skin conditioning solvents viscosity controlling agents

Fragrance Chemical	21 CFR	IID	Other
	582: SUBSTANCES GENERALLY RECOGNIZED AS SAFE § 582.1666 - Propylene glycol. § 582.4666 - Propylene glycol. **Registry of Toxic Effects of Chemical Substances (RTECS)** https://www.cdc.gov/niosh-rtecs/TY1E8480.html European Food Safety Authority (EFSA) reference(s): https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5235		Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ May cause primary skin irritation in some people, possibly due to dehydration, but the material is not a sensitizer. Cavender FL, Sowinski EJ; Patty's Toxicology CD-ROM (2005). NY, NY: John Wiley & Sons; Glycols. Online Posting Date: April 16, 2001 Percutaneous absorption may occur following application to damaged skin ... Goldfrank LR et al; Goldfrank's Toxicologic Emergencies 7th Ed., McGraw-Hill, New York, N.Y. p.841 (2002) Propylene glycol undergoes metabolic oxidation to pyruvic acid, acetic acid, lactic acid, and propionaldehyde. IPCS; Poisons Information Monograph 443; Propylene glycol (May 1994). Available from, as of January 4, 2009: http://www.inchem.org/documents/pims/chemical/pim443.htm Absorption of orally administered propylene glycol from the gastrointestinal tract, and its removal from the body, follow first order kinetics. Clearance from blood is rapid in humans, with a mean half-life of approx. 2 hr. Its metabolism is inhibited by pyrazole, indicating a role for alcohol dehydrogenase in this process. Once absorbed it is readily converted into lactic and pyruvic acids, which then enter the general metabolic pool. Organization for Economic Cooperation and Development; Screening Information Data Set for 1,2-Dihydroxypropane (57-55-6) p.20 (2001). Available from, as of December 31, 2009: http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html Toxicology and Applied Pharmacology. Vol. 45, Pg. 362, 1978. Raw Material Data Handbook, Vol.1: Organic Solvents. 1974. Vol. 1, Pg. 101, 1974. National Technical Information Service. Vol. PB280-477
TBHQ (t-butyl hydroquinone) 2-tert-butylbenzene-1,4-diol	172: FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION § 172.185 - TBHQ.	Present in 2 drug products for vaginal administration at 0.02%	https://pubchem.ncbi.nlm.nih.gov/compound/16043

Fragrance Chemical	21 CFR	IID	Other
1948-33-0 **Antioxidant (not a fragrance)**	177: INDIRECT FOOD ADDITIVES: POLYMERS § 177.2420 - Polyester resins, cross-linked. European Food Safety Authority (EFSA) reference(s): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2016.4363/epdf http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/84.pdf		**H302+H312 (22.39%): Harmful if swallowed or in contact with skin [Warning Acute toxicity, oral; acute toxicity, dermal]** **H312 (27.89%): Harmful in contact with skin [Warning Acute toxicity, dermal]** **H315 (20.64%): Causes skin irritation [Warning Skin corrosion/irritation]** **H317 (32.21%): May cause an allergic skin reaction [Warning Sensitization, Skin]** **H319 (45.03%): Causes serious eye irritation [Warning Serious eye damage/eye irritation]** **328 Active BioAssay Results** Food Chem Toxicol. 1986 Oct-Nov;24(10-11):1063-5. Toxicology of tert-butylhydroquinone (TBHQ). Natl Toxicol Program Tech Rep Ser. 1997 May;459:1-326. NTP Toxicology and Carcinogenesis Studies of t-Butylhydroquinone (CAS No. 1948-33-0) in F344/N Rats and B6C3F(1) Mice (Feed Studies). Contact Dermatitis. 1997 Aug;37(2):92-3. Induction of contact sensitization to monotertiary butyl hydroquinone. Food Chem. 2014 Jun 15;153:315-20. doi: 10.1016/j foodchem.2013.12.087. Epub 2014 Jan 3. Cytotoxicity and DNA damage properties of tert-butylhydroquinone (TBHQ) food additive. Journal of the American Oil Chemists' Society. Vol. 52, Pg. 53, 1975. Drug and Chemical Toxicology. Vol. 7, Pg. 335, 1984.
Terpineol	Present in Baby Powder Product. Refer to Table above.		
Trichloromethyl Phenyl Carbinyl Acetate rose acetate (2.2.2-trichloro-1-phenylethyl) acetate	Could Not Locate in 21 CFR UNII: 4VE62Y0O29 Could not locate EFSA references	Not Listed	https://pubchem.ncbi.nlm.nih.gov/compound/7007 **Xi - Irritant** **R 36/38 - Irritating to skin and eyes.** **H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation]**

Fragrance Chemical	21 CFR	IID	Other
90-17-5	Could not locate FEMA monograph		**14 Active BioAssay Results** Fragrance Chemicals of Concern Present on the IFRA List 2015: https://www.womensvoices.org/fragrance-ingredients/fragrance-chemicals-assigned-the-signal-word-warning-by-un-ghs/ Food and Cosmetics Toxicology. Vol. 13, Pg. 919, 1975.
Tromethamine 2-amino-2-(hydroxymethyl)propane-1,3-diol 77-86-1 Tromethamine, also known as trometamol or tham, belongs to the class of organic compounds known as 1, 2-aminoalcohols. These are organic compounds containing an alkyl chain with an amine group bound to the C1 atom and an alcohol group bound to the C2 atom. Tromethamine is a drug which is used for the prevention and correction of metabolic acidosis. **This is not a fragrance. Does not appear to be approved for food use.**	522: IMPLANTATION OR INJECTABLE DOSAGE FORM NEW ANIMAL DRUGS § 522.690 - Dinoprost. § 522.1002 - Follicle stimulating hormone. Could not locate EFSA references No FEMA Monograph No IFRA Standard	Approved as a drug product for the prevention and correction of metabolic acidosis. http://s3-us-west-2.amazonaws.com/drugbank/fda_labels/DB03754.pdf?1445015757 Present in 34 drug products for IV, IM, Intratympanic, Ophthalmic, Oral, Rectal, Respiratory, Subcutaneous, Topical, Transdermal and urethral administration.	https://pubchem.ncbi.nlm.nih.gov/compound/6503 **H315 (99.85%): Causes skin irritation [Warning Skin corrosion/irritation]** **H319 (100%): Causes serious eye irritation [Warning Serious eye damage/eye irritation]** **6 BioAssay Results** Cosmetic Uses: buffering agents masking agents Tromethamine is substantially eliminated by the kidneys. ... Ionized tromethamine (chiefly as the bicarbonate salt) is rapidly and preferentially excreted in urine at a rate that depends on the infusion rate. The manufacturer states that urinary excretion continues over a period of 3 days; 75% or more appears in the urine after 8 hours. In some studies, 50-75% of an iv dose was recovered in urine within 24 hours, but another study reported recovery in healthy adults to be 64% and 77% after 2 and 3 days, respectively. McEvoy, G.K. (ed.). American Hospital Formulary Service. AHFS Drug Information. American Society of Health-System Pharmacists, Bethesda, MD. 2007., p. 2647 Journal of Industrial Hygiene and Toxicology. Vol. 22, Pg. 315, 1940. Acta Biologica et Medica Germanica. Vol. 17, Pg. 217, 1966.

APPENDIX C

Currivulum Vitae

Michael M. Crowley, Ph.D.

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mcrowley@theridian.com

I. PERSONAL

Date of Birth:	February 24, 1966
Place of Birth:	Creve Coeur, MO, USA
Citizenship:	United States of America
Marital Status:	Married; Three Children

II. EDUCATION

The University of Texas at Austin, Austin, TX — 1/00 to 4/03
Ph.D. in Molecular Pharmaceutics, supervised by Dr. James W. McGinity,
Dissertation Title: "Physicochemical and Mechanical Characterization of Hot-Melt Extruded Dosage Forms"

Washington University, St. Louis, MO — 8/90 to 12/91
M.A., Organic Chemistry, *Cum Laude,* 3.3 GPA

University of Missouri, St. Louis, MO — 9/87 to 5/90
B.S., Chemistry, *Summa Cum Laude,* 3.88 GPA

III. WORK & RESEARCH EXPERIENCE

Theridian Technologies, LLC
President — **3/09 to Present**

Providing consulting services for drug product development and corporate / business development. Technical consulting services include product and process development, CMC project management, selection and management of CRO's / CMO's, application of proprietary and non-proprietary delivery technologies, scale up and technology transfer, and IP development. Scientific expert for patent litigation. Corporate and business development services include product and platform technology valuation and assessment, due diligence, strategy / tactics / planning, product and technology licensing and asset brokering.

Oticara, Inc. (formerly Oticus Labs, LLC)
Co-Founder — **1/15 to Present**

Specialty pharmaceutical company developing novel treatments for infectious disease.

Texas EnteroSorbents, Inc. ("TxESI")
Board of Directors **6/11 to Present**

TxESI was the first private company funded and owned by Texas A&M University System (TAMUS) based on innovative technology developed at TAMUS. TxESI products and technologies mitigate and/or remove toxins and inflammatory products from numerous animals and in humans. TxESI technologies, when included in food or animal feed, can prevent bacterial and fungal contamination. These unique compositions facilitate the removal of previously absorbed toxins and toxins associated with bacterial death and disease from the gastrointestinal tract.

PharmaForm, LLC
Vice President, Business Development **5/06 to 3/09**

Responsible for new and existing business development activities including management of sales, marketing, advertising and contract generation / negotiation. Contracts include proposals, development / service agreements, term sheets, license agreements and CDA's. Assess resource requirements for new and existing projects. Identify marketing opportunities and represent the company at trade shows and conventions. Identify, generate and coordinate intellectual property applications and filings with internal resources and attorneys. Manage and coordinate company sales, marketing and advertising efforts. Managed 4 employees. Closed $28M in contracts last 2 years, in-licensed 2 drug delivery technologies, executed 2 out-license agreements and 1 option agreement, and increased sales contracts an average of 28% per year and backlog an average of 12% per year.

PharmaForm, LLC
Vice President, Quality Control & Analytical R&D **5/05 to 5/06**

Responsible for management of the Quality Control Laboratory and Analytical Research & Development Laboratory. These labs develop methodology to analyze raw materials, API's, in process samples, bulk and finished product in a GMP environment. Additional scientific responsibilities include studying physical and chemical interaction between the pharmaceutical raw excipients and drug substances, development and validation of stability indicating analytical methodology and development of cleaning methodology to support clinical and commercial manufacturing. Managed 36 employees.

PharmaForm, LLC
Vice President, Drug Delivery Technology & Manufacturing Services **4/03 to 5/05**

Responsible for management of multiple customer oriented drug development projects from pre-formulation to clinical trials and commercial production, including identification of manufacturing equipment and process technology, scale up studies and trouble shooting. Products under development include solid oral dosage forms, transdermal, trans-mucosal, semi-solid and liquids of both small and large compounds. Managed 24 employees. Developed two products resulting in the company's first two out-licensing agreements. Responsible for the technical transfer and contract manufacture of the company's first commercial product and resulting PAI.

The University of Texas at Austin **1/00 to 4/03**
Graduate Student & Teaching Assistant

Responsibilities involved class work and planning experiments in support of a Ph. D. dissertation in Pharmaceutics. Experienced in hot-melt extrusion, wet granulation, extrusion / spheronization, fluidized bed granulating and coating, film coating and tableting. Analytical techniques encompassed USP test methodology including HPLC, GPC, x-ray

diffraction, scanning electron microscopy and differential scanning calorimetry. As lead TA for the undergraduate Compounding Laboratory, teaching responsibilities involved writing quizzes, midterms, finals exams, arranging 22 preparations for the semester, preparing a pre-lab discussion and demonstration each week, and evaluating the students work. Additionally, I supervised two undergraduates as part of an industry sponsored internship.

Mission Pharmacal Co., San Antonio, TX **7/95 to 1/00**
Research & Development, Operations Manager

Responsible for product and process development for both nutritional supplements and drug products (NDA, 505B2, ANDA) in solid oral and topical dosage forms. Duties included pre-formulation, formulation and product development, analytical and physico-chemical characterization, scale-up, packaging engineering, validation and troubleshooting under GMPs. Generated data and documents for CMC section of regulatory filings. Evaluated and reviewed products in stability programs to support development activities, clinical trials and regulatory submissions. Experimental data and reports were presented in technical reports and oral presentations to senior management. Managed 16 - 24 employees.

Warner-Jenkinson Company Inc., St. Louis, MO **1/92 to 7/95**
Chemist, Pharmaceuticals

Managed pharmaceutical projects involving the application of excipients in film coating, tablets, pellets, solutions, suspensions, topicals, printing inks and medical devices. Other responsibilities included writing technical data bulletins, developing analytical methods and product brochures, maintaining regulatory information, determining product pricing, making field service calls and representing the company at trade shows and conventions.

Sigma Chemical Company, St. Louis, MO **5/90 to 8/90**
Analyst, Summer Intern

I worked as a summer intern and analyst in the Product Assay Laboratory. Responsible for all flame emission, atomic absorption and atomic fluorescence spectrometry for the Sigma product line. The instrument was computer interfaced and employed a Zeeman Effect background correction using standard atomization and electrothermal methods. Programmed the computer for statistical analysis of calibration curves, sample preparation and instrumental performance.

University of Missouri, St. Louis, MO **5/89 to 5/90**
Undergraduate Research Associate

The topic of my undergraduate research was the thermodynamics of binding to transferrin. Binding coefficients are needed for the rational design of pharmaceutical chelating agents, which must be able to compete with transferrin in vivo. The binding coefficients were evaluated by direct titration of metal free protein with metals and/or anionic ligands as measured by UV/Vis spectrometry. Nonlinear least squares refinement of the observed data yielded binding coefficients. The results of our research were published in *Inorganic Chemistry*.

Monsanto Co., St. Louis, MO **5/88 to 12/89**
Animal Sciences Division, Formulations Chemistry, Research Analyst

Responsible for generation of data using analytical methods: HPLC, SE-HPLC, atomic absorption, UV/Vis spectrometry, in vitro dissolution, particle size determination by laser light diffraction, viscometry, fluorimetry, moisture content by Karl Fischer and several wet techniques. Trained in GLP/GMP operations and analytical method

validations in support of clinical trials and stability studies for somatotropin proteins. Trained and qualified other analysts in analytical methods, equipment operations and troubleshooting.

IV. PROFESSIONAL MEMBERSHIPS

1. American Association of Pharmaceutical Scientists
   (Sections of Pharmaceutical Technology, Pharmaceutics and Drug Delivery)
2. Controlled Release Society
3. American Chemical Society (past)
4. Licensing Executives Society (past)

V. RESEARCH INTERESTS

1. Development of novel drug delivery systems.
2. Sustained release oral dosage forms and mechanism(s) of drug release.
3. Melt extrusion and thermal processing techniques.
4. Solubility enhancement, particle engineering, microencapsulation and emulsion techniques.
5. Bioadhesive drug delivery systems.
6. Novel controlled release film coating formulations using acrylic and cellulosic polymers.
7. Analytical characterization and stability of active pharmaceutical agents and excipients.

VI. COURSES PRESENTED

1. Pharmaceutics I Laboratory – The University of Texas at Austin.
2. Chemistry I Laboratory – Washington University.

VII. HONORS & AWARDS

2012 "Most Downloaded Manuscript Published in Drug Development & Industrial Pharmacy" Award for M.M. Crowley, F. Zhang, et al, "Pharmaceutical Applications of Hot-Melt Extrusion: Part I", Drug Development and Industrial Pharmacy, 33 (9): 909-926 (2007)
2011 "Most Downloaded Manuscript Published in Drug Development & Industrial Pharmacy" Award for M.M. Crowley, F. Zhang, et al, "Pharmaceutical Applications of Hot-Melt Extrusion: Part I", Drug Development and Industrial Pharmacy, 33 (9): 909-926 (2007)
2002 – 2003 University Continuing Fellow, the University of Texas at Austin
2002 – 2003 American Foundation for Pharmaceutical Education Fellow
2001 – 2002 Texas Excellence in Teaching Award
2001 – 2002 American Society for Quality Control Scholarship
2001 – 2002 American Foundation for Pharmaceutical Education Fellow
1990 – 1991 Washington University Full Tuition Scholarship
1990 – 1991 Washington University Fellow
1988 – 1990 University of Missouri Scholars Scholarship
1990 American Institute of Chemists Outstanding Senior Award
1990 Alan F. Berndt, Ph.D. Outstanding Senior in Chemistry Award
1989 – 1990 Eric G. Brunngraber, Ph.D. Undergraduate Research Fellowship
1989 American Chemical Society Outstanding Chemical Technology Student Award

VIII. CONTRIBUTIONS TO SCIENTIFIC LITERATURE

1. Journal of Pharmaceutical Sciences – referee.
2. Drug Development and Industrial Pharmacy – referee.
3. European Journal of Pharmaceutics and Biopharmaceutics – referee.
4. Journal of Pharmacy and Pharmacology – referee.
5. European Journal of Pharmaceutics – referee.
6. Pharmaceutical Research – referee.
7. International Journal of Pharmaceutics – referee.
8. Journal of Microencapsulation – referee.
9. S.T.P. Pharma Sciences (France) – referee.
10. Pharmaceutical Development and Technology – referee.
11. Journal of Controlled Release – referee.
12. AAPS PharmSciTech – referee.

IX. PUBLICATIONS

1. WR Harris, PK Bali, MM Crowley, "Kinetics of Iron Removal from Monoferric and Cobalt-Labeled Monoferric Transferrins by Diethylenetriaminepenta (methylenephosphonic acid) and Diethylenetriaminepentaacetic Acid", Inorganic Chemistry, 1992; 31: 2700 - 2705.
2. MM Crowley, F Zhang, JJ Koleng, JW McGinity, "Stability of Polyethylene Oxide in Matrix Tablets Prepared by Hot-Melt Extrusion", Biomaterials, 2002; 23(21): 4241 – 4248.
3. MM Crowley, B Schroeder, A Fredersdorf, S Obara, M Talarico, S Kucera, JW McGinity, "Physicochemical Properties and Mechanism of Drug Release from Ethyl Cellulose Matrix Tablets prepared by Direct Compression and Hot-melt Extrusion", International Journal of Pharmaceutics, 2004; 269(2): 509 – 522.
4. MM Crowley, A Fredersdorf, B Schroeder, S Prodduturi, MA Repka, JW McGinity, "The Influence of Guaifenesin and Ketoprofen on the Properties of Hot-melt Extruded Polyethylene Oxide Films", European Journal of Pharmaceutical Science, 2004; 22(5): 409 – 418.
5. S Venkata, S Tumuluri, S Prodduturi, MM Crowley, BA Avery, MA Repka, JW McGinity, "The Use of Near-Infrared Spectroscopy for The Quantitation of An Active In Hot-Melt Extruded Films", Drug Development and Industrial Pharmacy, 2004; 30(5): 505-511.
6. CR Young, MM Crowley, JW McGinity, "Physicochemical properties and film-coating of a melt-extruded and spheronized solid dispersion for pH-dependent drug delivery", Journal of Microencapsulation, 2007; 24(1): 57-71.
7. MM Crowley, F Zhang, MA Repka, S Thumma, SB Upadye, S Kumar, JW McGinity, C Martin, "Pharmaceutical Applications of Hot-Melt Extrusion: Part 1", Drug Delivery & Industrial Pharmacy, 2007; 33(9): 909-926.
8. MA Repka, S Thumma, SB Upadye, S Kumar, MM Crowley, F Zhang, C Martin, JW McGinity, "Pharmaceutical Applications of Hot-Melt Extrusion: Part 2", Drug Delivery & Industrial Pharmacy, 2007; 33(10) 1043-1057.

9. KA Overhoff, R Clayborough, MM Crowley, "Review of the TAIFUN® Multi-dose Dry Powder Inhaler Technology", Drug Delivery & Industrial Pharmacy, 2008; 34(9) 960 – 965.

10. C Berkland, G Laurence, S Lermer and MM Crowley, "An Overview of the NanoCluster Powder Formulation Technology", Pharmaceutical Technology, 2010 34(10) 72-78.

11. T Listro, M Borek, MM Crowley, K Nollenberger, "Analytical Tools & Techniques in Hot Melt Extrusion & Case Studies on Formulation Development & Process Scale-Up" Drug Development & Delivery, 2012 12(7) 36-40.

12. SA. Kucera, MS Zamloot, MM Crowley, LH Burns, N Friedmann and R Barbier. Abuse-deterrent properties of REMOXY® ER, a high-viscosity extended-release oxycodone formulation. Journal of Opioid Management. *In press.*

X. BOOK CHAPTERS

1. M.M. Crowley. "Solutions, Emulsions, Suspensions and Extracts" in Remington: The Science and Practice of Pharmacy, 21st Edition. Edited by R. Hendrickson. Lippincott, Williams & Wilkins (2005).

2. M.M. Crowley. "Solutions, Emulsions, Suspensions and Extracts" in Remington: The Science and Practice of Pharmacy, 22nd Edition. Edited by R. Hendrickson. Pharmaceutical Press, (2013).

3. M.M. Crowley. "Solutions, Emulsions, Suspensions and Extracts" in Remington: Essentials of Pharmaceutics, 1st Edition. Edited by L. Felton. Pharmaceutical Press, (2013).

4. M.M. Crowley. "Pharmaceutical Dosage Forms: Manufacturing and Compounding" in Remington: An Introduction to Pharmacy, 1st Edition. Edited by L.V. Allen. Pharmaceutical Press, (2013).

XI. PRESENTATIONS & INVITED LECTURES

1. CA Signorino, MM Crowley, L Forcellini, "Assessing the Uniformity of Aqueous Film Coatings Applied to Compressed Tablets", Ninth Annual Meeting, Proceedings of the American Association of Pharmaceutical Scientists, San Diego, CA., November, 1994.

2. MM Crowley, F Zhang, JJ Koleng, JW McGinity, "Evaluation of a Hot-Melt Extrusion Technique using a Hydrophilic Thermal Polymer and Retardant for the Preparation of Extended Release Chlorpheniramine Maleate Tablets", Fourteenth Annual Meeting, Proceedings of the American Association of Pharmaceutical Scientists, Indianapolis, Indiana. October, 2000.

3. MM Crowley, "Properties of Hot-Melt Extruded CPM Tablets Using Hydrophilic Polymers", Seminar, College of Pharmacy Fall 2000 Pharmaceutics Seminar Series, The University of Texas at Austin, Austin, Texas. November, 2000.
4. MM Crowley, "Properties of Potassium Chloride Controlled Release Dosage Forms", Seminar, College of Pharmacy Spring 2001 Pharmaceutics Seminar Series, The University of Texas at Austin, Austin, Texas. April, 2001.

5. KA Overhoff, DP Jones, JR Hunt, LD Bruce, MM Crowley, CR Young, JW McGinity, "Influence of pH, Neutralizing Agent, Storage Temperature and Packaging on the Stability of Methylparaben and Propylparaben in a Hydrophilic Gel", Fifteenth Annual Meeting, Proceedings of the American Association of Pharmaceutical Scientists, Denver, CO. October, 2001.
6. MM Crowley, F Zhang, JJ Koleng, JW McGinity, "The Stability of Polyethylene Oxide in Matrix Tablets Prepared by Hot-Melt Extrusion", Fifteenth Annual Meeting, Proceedings of the American Association of Pharmaceutical Scientists, Denver, CO. October, 2001.
7. MM Crowley, S Obara, JW McGinity, "The Influence of Low Substituted Hydroxypropyl Cellulose on the Properties of Hot-Melt Extruded Tablets, Fifteenth Annual Meeting, Proceedings of the American Association of Pharmaceutical Scientists, Denver, CO. October, 2001.
8. S Prodduturi, MM Crowley, SP Stodghill, MA Repka, "Solid State Characterization of Hot-Melt Extruded Films Containing Clotrimazole", Sixteenth Annual Meeting, Proceedings of the American Association of Pharmaceutical Scientists, Toronto, Ontario, Canada. October, 2002.

9. MM Crowley, A Fredersdorf, B Schröder, S Obara, S Kucera, JW McGinity, "Properties of Ethyl Cellulose Matrix Tablets", Sixteenth Annual Meeting, Proceedings of the American Association of Pharmaceutical Scientists, Toronto, Ontario, Canada. October, 2002.

10. MM Crowley, MA Repka, B Avery, V Tumuluri, S. Prodduturi, "The Use Of Near-infrared Spectroscopy For The Quantitation Of An Active In A Hot-melt Extruded Film" Seventeenth Annual Meeting, Proceedings of the American Association of Pharmaceutical Scientists, Salt Lake City, Utah. October, 2003.

11. S Prodduturi, MM Crowley, MA Repka, "Influence Of Water-soluble Polymeric Matrix Carriers On The Bioadhesive And Release Properties Of Hot-melt Extruded Films Containing A Water Insoluble Drug", Seventeenth Annual Meeting, Proceedings of the American Association of Pharmaceutical Scientists, Salt Lake City, Utah. October, 2003.

12. M Kemper, I Lewis, S. Prodduturi, V. Tumuluri, MM Crowley, B. Avery, MA Repka, "The Use Of Off-line And On-line Raman Spectroscopy To Quantify Ketoprofen And Clotrimazole In Hot-melt Extruded Film Formulations", Seventeenth Annual Meeting, Proceedings of the American Association of Pharmaceutical Scientists National Meeting, Salt Lake City, Utah. October, 2003.

13. JW McGinity, CR Young, M Cerea, MM Crowley, "Properties Of Film-coated Polyethylene Oxide Pellets Prepared By A Hot-melt Extrusion And Spheronization Process", Seventeenth Annual Meeting, Proceedings of the American Association of Pharmaceutical Scientists National Meeting, Salt Lake City, Utah. October, 2003.

14. J.W. McGinity, CR Young, M Cerea, MM Crowley, C Dietzsch, T. Farrell, K. Fegely, "Properties Of Acryl-eze® Matrix Tablets Prepared Using A Hot-melt Extrusion Process", Seventeenth Annual Meeting, Proceedings of the American Association of Pharmaceutical Scientists National Meeting, Salt Lake City, Utah. October, 2003.

15. C. Dietzsche, D. Sauer, CR Young, MM Crowley, J.W. McGinity, "Physicochemical Properties of Film-Coated Melt-Extruded Pellets", Proceedings of the 15th International Symposium on Microencapsulation, Parma, Italy. September, 2005.

16. Pharmaceutical Applications of Hot-Melt Extrusion, Leistritz Pharmaceutical Extrusion Seminar, Bridgewater, New Jersey. June, 2007.

17. "Pharmaceutical Applications of Hot-Melt Extrusion", Proceedings of the 12th Annual Drug Delivery Technologies & Deal-Making, New Brunswick, New Jersey. September, 2007.

18. Drug Delivery Executive Interview, Drug Delivery Technology, April, 2008 Volume 8, Number 4, pages 50 – 52.

19. "Physical and Chemical Properties of Hot-Melt Extruded Dosage Forms", Leistritz Pharmaceutical Extrusion Seminar, Bridgewater, New Jersey. June, 2008.

20. "Business Development in the Pharmaceutical Industry", Contemporary Drug Development Seminar, Course UG302, The University of Texas at Austin, Austin, Texas. October, 2009.

21. "Shape of Innovation: Polymer Processing and New Product Possibilities", Leistritz Pharmaceutical Extrusion Seminar, Bridgewater, New Jersey. June, 2013.

22. "Applications of Hot Melt Extrusion: Pharmaceutical Products and Medical Devices", The University of Houston, College of Pharmacy Invited Speaker Series, Houston, TX. March, 2014

23. AE. Listro, MM Crowley, T. Appleton, LA. Acquarulo. "A Comparison of Saturated Solubility Enhancement via Spray Drying and Hot Melt Extrusion Processing", 9th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Lisbon, Portugal. April, 2014.

24. "Melt Coextrusion for Special Drug Products." St. John's University, College of Pharmacy and Health Sciences, The 8th Annual Charles Jarowski Industrial Pharmacy Symposium. Queens, New York June 17, 2015.

25. AE Listro, A Miller, F Zhang, MM Crowley, LA Acquarulo. "Effect of Processing Methods on Physical Stabilities of Amorphous Solid Dispersions Consisting of Naproxen and Povidone" Controlled Release Society 2015 Annual Meeting, Edinburgh, Scotland, July, 2015.

26. "Rapid Screening Techniques and Polymer Considerations for Hot Melt Extruded Amorphous Solid Dispersions" 2015 Dow Solubility Symposium. Collegeville, PA October 6, 2015.

27. A. Miller, T. Listro, M Crowley, F. Zhang and L. Acquarulo, "The Effect of Processing Methods on Physical Stability of Amorphous Solid Dispersions Consisting of Naproxen and Povidone" Twenty-ninth Annual Meeting, Proceedings of the American Association of Pharmaceutical Scientists National Meeting, Orlando, FL. October, 2015.

28. A. Miller, T. Listro, M Crowley, F. Zhang and L. Acquarulo, "A Novel Analytical Method Based On Ultrafiltration Technique Has Been Developed To Measure The Free Drug Concentration In Aqueous Medium Containing Amorphous Solid Dispersions" Twenty-ninth Annual Meeting, Proceedings of the American Association of Pharmaceutical Scientists National Meeting, Orlando, FL. October, 2015.

29. "Business Development in the Pharmaceutical Industry", Interdisciplinary Collaboration and Career Development, Course PGS 191Q, The University of Texas at Austin, Austin, Texas. February, 2017.

30. "Business Development in the Pharmaceutical Industry", Interdisciplinary Collaboration and Career Development, Course PGS 192Q, The University of Texas at Austin, Austin, Texas. February, 2018.

31. "Regulatory Affairs in Pharmaceutical Drug Development", Pharmaceutical Product Development, Course PGS 381F, The University of Texas at Austin, Austin, Texas. October, 2018.

XII. PATENTS & PATENT APPLICATIONS

1. C.R. Young, M.M. Crowley, T.P. Farrell, K.A. Fegely, J.W. McGinity. "Method for Preparing Thermoformed Compositions Containing Acrylic Polymer Binders, Pharmaceutical Dosage Forms and Methods of Preparing the Same". U.S. Provisional Patent Application Number 2004/014109.

2. J.J. Koleng and M.M. Crowley. "Compressed Composition Comprising Magnesium Salt", U.S. Patent Application Number 20050220865 BPH-1 (Serial 10-816,771); International Patent Application Number BPH-3 (PCT/US05/10979).

3. M. M. Crowley, F. Zhang, J. J. Koleng and J. Keen, "Process For The Preparation Of A Hot-Melt Extruded Laminate", U.S. Patent No. 8,465,759.

4. M. M. Crowley, F. Zhang, J. J. Koleng and J. Keen, "Hot Melt Extruded Transdermal Compositions Containing Testosterone", Filed March, 2006, U.S. Provisional Application for Patent No. 60/785,501.

5. M. M. Crowley, F. Zhang, J. J. Koleng and J. Keen, "Stabilized Compositions Containing Alkaline Labile Drugs", U.S. Patent No. 8,173,152; EP 2,010,156

6. M. M. Crowley, F. Zhang, J. J. Koleng and J. Keen, "Hydrophobic Abuse Deterrent Delivery System", Filed July 21, 2006, U.S. Provisional Application for Patent No. 60/820,091.

7. J.M. Vaughn, M. M. Crowley, F. Zhang, J. J. Koleng, J. Keen and J.R. Hughey, "Hydrophobic Opioid Abuse Deterrent Delivery System Using Opioid Antagonists", Filed July 20, 2007, U.S. Provisional Application for Patent No. 20080075768.

8. M. M. Crowley, F. Zhang, J. J. Koleng and J. Keen, "Hydrophilic Abuse Deterrent Delivery System", Filed August 30, 2006, U.S. Provisional Application for Patent No. 60/824057.

9. J.M. Vaughn, M. M. Crowley, F. Zhang, J. J. Koleng, J. Keen and J.R. Hughey, "Hydrophilic Opioid Abuse Deterrent Delivery System Using Opioid Antagonists", Filed July 20, 2007, U.S. Provisional Application for Patent No. 20080075771.

10. M. M. Crowley, F. Zhang, J. Vaughn and J. J. Koleng, Bioadhesive Film Drug Delivery System", Filed August 30, 2006, U.S. Provisional Application for Patent No. 60/824059.

11. M. M. Crowley, F. Zhang, J. J. Koleng, J. Keen, J. Vaughn, J Hughey. "Hydrophobic Abuse Deterrent Delivery System For Hydromorphone," Filed July 20, 2007, U.S. Provisional Application for Patent No. 2008/0020032.

12. A. Grattoni, E. de Rosa, R. Goodall, L. Hudson, M. Crowley. "Device And Method For Sustained Release Of Therapeutic Agent" U.S. Provisional Application filed October 24, 2011.

13. M.M. Crowley, R. Goodall, L. Hudson. "Device And Method For Sustained Release Of Low Water Solubility Therapeutic Agent In Solubilizer" U.S Provisional Application Serial No 61/864,768 filed August 12, 2013.

14. M. M. Crowley, J. Keen, J.J. Koleng and F. Zhang, "Stabilized Compositions Containing Alkaline Labile Drugs", U.S. Patent No. 8,883,187.

15. M. M. Crowley, J. Keen, J.J. Koleng and F. Zhang, "Stabilized Compositions Containing Alkaline Labile Drugs", U.S. Patent No. 9,364,445.

16. M. M. Crowley, J. Keen, J.J. Koleng and F. Zhang, "Stabilized Compositions Containing Alkaline Labile Drugs", U.S. Patent No. 9,867,786.